Australian Government
Department of Health
Office of the Gene Technology Regulator

Risk Assessment and Risk Management Plan (Consultation version) for

DIR 182

Commercial supply of recombinant COVID-19 vaccine

Applicant: Janssen-Cilag Pty Ltd

24 February 2021

This RARMP is open for consultation until 30 March 2021.

Written comments on the risks to human health and safety and the environment posed by this proposed supply of the GM COVID-19 vaccine are invited. You may make your submission

via mail to: The Office of the Gene Technology Regulator, MDP 54 GPO Box 9848, Canberra ACT 2601

or

via email to: ogtr@health.gov.au.

Please note that issues regarding patient safety and the quality of the vaccine **do not** fall within the scope of these evaluations as they are the responsibilities of other agencies and authorities.

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Summary of the Risk Assessment and Risk Management Plan

(Consultation Version) for

Licence Application DIR 182

Introduction

The Gene Technology Regulator (the Regulator) has received a licence application (DIR 182) for import, transport, storage and disposal of a genetically modified (GM) COVID-19 vaccine, as part of its commercial supply as a human vaccine. These activities are classified as Dealings involving the Intentional Release (DIR) of genetically modified organisms into the Australian environment under the *Gene Technology Act 2000*.

Before the GM vaccine can be used, Janssen-Cilag Pty Ltd must also obtain regulatory approval from the Therapeutic Goods Administration (TGA). Therapeutic goods for sale in Australia must be included in the Australian Register of Therapeutic Goods (ARTG) under the *Therapeutic Goods Act 1989*. The TGA will be responsible for assessing patient safety; quality and efficacy of the vaccine prior to including the GM vaccine on the ARTG. In addition, approval from the Department of Agriculture, Water and the Environment will also be required for the importation of the GM vaccine.

The Regulator has prepared a Risk Assessment and Risk Management Plan (RARMP) for this application, which concludes that the proposed supply of the GM vaccine poses negligible risks to human health and safety and the environment. Licence conditions have been drafted for the proposed supply. The Regulator invites submissions on the RARMP, including draft licence conditions, to inform the decision on whether or not to issue a licence.

The application

Application number	DIR-182
Applicant	Janssen-Cilag Pty Ltd
Project title	Commercial supply of recombinant COVID-19 vaccine (Ad26.COV.S)
Parent organism	Human adenovirus 26

Introduced gene and modified trait	• Deletion of:
	  ○ E1 gene (renders virus unable to multiply)
	  ○ E3 gene (increases immune response to virus and virus production during manufacture)
	• Partial substitution of E4 gene with the corresponding gene from the human adenovirus 5 (improves virus yield during manufacture)
	• Insertion of a gene based on the SARS-CoV-2 spike protein (expresses spike protein)

Approved clinical trials	Phase I, I/II and III clinical trials with the GM vaccine Ad26.CoV2.S (also known as JNJ-78436735, Ad26COVS1 or VAC31518) are currently being conducted in several countries including the United States, Belgium, Columbia, France, Germany, Japan, Philippines, South Africa, Spain and the United Kingdom to assess the safety and efficacy of the vaccine in adults between 18-55 years and over 65 years.
Current approvals	• The GM vaccine is currently not approved for commercial supply in any region or country.
Proposed locations	Australia-wide

Primary purpose	Commercial supply of the GM COVID-19 vaccine

Risk assessment

The risk assessment concludes that risks to the health and safety of people or the environment from the proposed short or long term supply are negligible. No specific risk treatment measures are required to manage these negligible risks.

The current assessment focuses on risks posed to people other than the intended vaccine recipient and to the environment, which may arise from the import, transport, storage or disposal of the GMO. The risk assessment process considers how the genetic modification and activities conducted with the GM vaccine in the context of import, transport, storage and disposal might lead to harm to people or the environment. Risks are characterised in relation to both the seriousness and likelihood of harm, taking into account information in the application, relevant previous approvals, current scientific knowledge and advice received from a wide range of experts, agencies and authorities consulted on the preparation of the RARMP. Both the short and long term risks were considered.

Credible pathways to potential harm that were considered include the; potential exposure of people and animals to the GMO; the potential for the GMO to recombine with other similar viruses or to get genes from those viruses; and the potential for the GMO to integrate into the host genome. The potential for the GMO to be released into the environment and its effects were also considered.

The principal reasons for the conclusion of negligible risks associated with import, transport, storage and disposal of the GMO are:

- The GMO is replication incompetent which will prevent it from multiplying in other cells;
- The GMO would be restricted to the site of injection and/or draining lymph nodes and would not be shed from the vaccine recipients;
- The likelihood of accidental exposure to the GMO in people not being vaccinated (non-vaccinees) would be minimised due to well-established import, transport, storage and disposal procedures; and
- The likelihood of complementation and recombination of GMO with other adenoviruses is very low.

Risk management

The risk management plan concludes that risks from the proposed dealings can be managed so that people and the environment are protected by imposing general conditions to ensure that there is ongoing oversight of the vaccine containing the GMO.

Risk management is used to protect the health and safety of people and to protect the environment by controlling or mitigating risk. The risk management plan evaluates and treats identified risks and considers general risk management measures. The risk management plan is given effect through licence conditions.

As the level of risk was assessed as negligible, specific risk treatment is not required. However, the Regulator has drafted licence conditions regarding post-release review (post-market surveillance) to ensure that there is ongoing oversight of the supply of the GM COVID-19 vaccine and to allow the collection of ongoing information to verify the findings of the RARMP. The draft licence, detailed in Chapter 4 of the consultation RARMP, also contains a number of general conditions relating to ongoing licence holder suitability, auditing and monitoring, and reporting requirements, which include an obligation to report any unintended effects.

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Abbreviations

AICIS	Australian Industrial Chemicals Introduction Scheme
AdV	Adenovirus
APVMA	Australian Pesticides and Veterinary Medicines Authority
AQIS	Australian Quarantine and Inspection Service
ARTG	Australian Register of Therapeutic Goods
CAR	Coxsackie and adenovirus receptor
COVID-19	Coronavirus infectious disease 2019
DAWE	Department of Agriculture, Water and the Environment
DIR	Dealings involving Intentional Release
DNA	Deoxyribonucleic acid
EU	European Union
FSANZ	Food Standards Australia New Zealand
g	gram
GM	Genetically modified
GMO	Genetically modified organism
GP	General practitioners
GTTAC	Gene Technology Technical Advisory Committee
HAdV	Human adenovirus
HGT	Horizontal gene transfer
IATA	International Air Transport Association
IM	Intramuscular
kb	Kilobase pair of DNA
LGA	Local government area
Mb	Mega base pairs
min	Minute
ml	Milli litre
NSW	New South Wales
OGTR	Office of the Gene Technology Regulator
Orf	Open reading frame
PCR	Polymerase chain reaction
QLD	Queensland
RARMP	Risk Assessment and Risk Management Plan
RNA	Ribonucleic acid
S	Spike
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
TGA	Therapeutic Goods Administration
the Act	The *Gene Technology Act 2000*
the Regulations	The Gene Technology Regulations 2001

the Regulator	The Gene Technology Regulator
tPA	Tissue plasminogen activator
UK	United Kingdom
USA	United States of America
WA	Western Australia
WHO	World Health Organization

Chapter 1 Risk assessment context

Section 1 Background

1. An application has been made under the *Gene Technology Act 2000* (the Act) for Dealings involving the Intentional Release (DIR) of genetically modified organisms (GMOs) into the Australian environment.

2. The Act and the Gene Technology Regulations 2001 (the Regulations), together with corresponding State and Territory legislation, comprise Australia's national regulatory system for gene technology. Its objective is to protect the health and safety of people, and to protect the environment, by identifying risks posed by or as a result of gene technology, and by managing those risks through regulating certain dealings with GMOs.

3. Section 50 of the Act requires that the Gene Technology Regulator (the Regulator) must prepare a Risk Assessment and Risk Management Plan (RARMP) in response to an application for release of GMOs into the Australian environment. Sections 50, 50A and 51 of the Act and sections 9 and 10 of the Regulations outline the matters which the Regulator must take into account and who must be consulted when preparing the RARMP.

4. The *Risk Analysis Framework* (RAF) (OGTR, 2013) explains the Regulator's approach to the preparation of RARMPs in accordance with the Act and the Regulations. The Regulator has also developed operational policies and guidelines that are relevant to DIR licences. These documents are available from the Office of the Gene Technology Regulator (OGTR website).

5. Figure 1 shows the information that is considered, within the regulatory framework above, in establishing the risk assessment context. This information is specific for each application. Risks to the health and safety of people or the environment posed by the proposed supply are assessed within this context. Chapter 1 describes the risk assessment context for this application.

RISK ASSESSMENT CONTEXT

The GMO
Modified genes
Novel traits

Parent organism (comparator)
Origin and taxonomy
Cultivation and use
Biology

Proposed GMO dealings
Activities
Limits
Controls

Previous releases
Australian approvals
International approvals

Receiving environment
Environmental conditions: abiotic and biotic factors
Production practices
Related organisms
Similar genes and proteins

Figure 1. Summary of parameters used to establish the risk assessment context, within the legislative requirements, operational policies and guidelines of the OGTR and the RAF.

6. This application does not meet the criteria for a limited and controlled release application under section 50A of the Act. Therefore, under section 50(3) of the Act, the Regulator was required to seek advice from prescribed experts, agencies and authorities on matters relevant to the preparation of the RARMP. This first round of consultation included the Gene Technology Technical Advisory Committee (GTTAC), State and Territory Governments, Australian Government authorities and agencies prescribed

in the Regulations and the Minister for the Environment. A summary of issues contained in submissions received is provided in Appendix A.

7. Section 52 of the Act requires the Regulator to seek comment on the RARMP from the experts, agencies and authorities outlined above, as well as the public through a second round of consultation.

1.1 Interface with other regulatory schemes

8. Gene technology legislation operates in conjunction with other regulatory schemes in Australia. The GMOs and any proposed dealings conducted under a licence issued by the Regulator may also be subject to regulation by other Australian government agencies that regulate GMOs or GM products, including Food Standards Australia New Zealand (FSANZ), the Australian Pesticides and Veterinary Medicines Authority (APVMA), the Therapeutic Goods Administration (TGA), the Australian Industrial Chemicals Introduction Scheme (AICIS) and the Department of Agriculture, Water and the Environment (DAWE).

9. The DAWE regulates products imported into Australia that could pose biosecurity risks to the environment under the *Biosecurity Act 2015*. Therefore, the importation of biological material such as live GM vaccines requires a permit from DAWE.

10. The TGA provides a national system of controls for therapeutic goods. It administers the provisions of the *Therapeutic Goods Act 1989* which specifies the standard that must be met before a vaccine can be registered on the Australian Register of Therapeutic Goods (ARTG). Inclusion in ARTG is required before a vaccine can be lawfully supplied in Australia. As part of this process, the TGA would assess the safety, quality and efficacy of the vaccine. Quality aspects could include batch-to-batch consistency of vaccine composition, purity and potency. Safety aspects could include toxicological and allergenicity profile of the vaccine, including any excipients, by-products and impurities from manufacture; and monitoring of serious adverse events.

11. The administration/use of GMOs as therapeutics is not regulated under gene technology legislation. The Regulator does not assess vaccine excipients and would not assess manufacturing by-products and impurities unless they are themselves GM products.

12. The labelling, handling, sale and supply of scheduled medicines is regulated through the *Scheduling Policy Framework for Medicines and Chemicals* (AHMAC, 2018). Guidelines for the safe handling, storage and distribution of Schedule 4 medicines such as vaccines are specified through the *Australian Code of good wholesaling practice for medicines in schedules 2, 3, 4 & 8* (TGA, 2011). The provisions of this Code, which ensure that quality is maintained during wholesaling, are applied through applicable State and Territory therapeutic goods/drugs and poisons legislation, and/or State or Territory wholesaler licensing arrangements.

13. To avoid duplication of regulatory oversight, risks that have been considered by other regulatory agencies would not be re-assessed by the Regulator.

14. For the commercial supply of a GM COVID-19 vaccine, dealings regulated under the Act include the import, transport, storage and disposal of GMOs. The Regulator has assessed risks to people as a consequence of conducting these activities and risks from persistence of the GMOs in the environment.

Section 2 The proposed dealings

15. SARS-CoV-2 is a novel coronavirus discovered in December 2019 in Wuhan, Hubei province of China and is the cause of the COVID-19 disease. The rapid spread of this virus around the world led the World Health Organization (WHO) to declare the outbreak as a public health emergency of international concern (PHEIC) on the 30th January 2020 and eventually a pandemic on 11th March 2020 (WHO - Timeline of WHO's response to COVID-19, 2020).

16. The most common symptoms of COVID-19 are fever, tiredness and a dry cough, although some patients develop aches and pains, nasal congestion, runny nose, sore throat or diarrhoea. Symptoms are usually mild with gradual onset and about 80% of infected people recover without specific treatment. However, COVID-19 can cause complications such as severe pneumonia, acute respiratory distress syndrome, and multiple organ failure and in some cases, death. This is especially in older patients and those with pre-existing respiratory or cardiovascular conditions. There is currently one vaccine available for COVID-19 in Australia but as of 9th February 2021, 63 candidate vaccines are in clinical evaluation around the world (WHO -Draft landscape of COVID-19 candidate vaccine, 2020). These vaccines are based on a variety of platforms such as lipid nanoparticles encapsulated mRNA, DNA, adjuvant protein, inactivated virus particles and non-replicating viral vectors.

17. Janssen-Cilag Pty Ltd (Janssen-Cilag) is seeking authorisation for the commercial supply of a genetically modified (GM) vaccine (Ad26.COV2.S) Australia-wide to prevent coronavirus infectious disease 2019 (COVID-19) caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

18. For the ongoing commercial supply of the GM vaccine, the dealings assessed by the Regulator are the:

(a) importation;

(b) transportation;

(c) disposal;

and possession (including storage), supply or use of the GMO for the purposes of, or in the course of, any of the above.

2.1 Details of the proposed dealings

19. The GM vaccine would be distributed to a variety of facilities which offer vaccination services in all Australian States and Territories, where it will be administered by intramuscular (IM) injection.

20. The vaccine would be supplied as a multi-dose glass vials with an extractable volume of 2.5ml (5 x 0.5 ml doses). These vials will be packed into cartons followed by packaging into shipping boxes for distribution.

21. The GM vaccine will be manufactured overseas and imported into Australia. An import permit from the DAWE would be required for the importation into Australia.

22. The storage and handling of the GM vaccine would be carried out by couriers experienced in the distribution of pharmaceutical products, such as live vaccines in accordance with the *Australian Code of Good Wholesaling Practice for Medicines in schedules 2, 3, 4 and 8* (TGA, 2011) and the WHO *Good distribution practices for pharmaceutical products* (WHO, 2010).

23. The transport within Australia (i.e., distribution to vaccination centres) would be conducted by a commercial courier company experienced in the transportation of pharmaceutical products such as live vaccines.

24. Storage of the GM vaccine at vaccination centres and other facilities will be conducted according to the *National Vaccine Storage Guidelines* (Department of Health, 2019) and the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP, 2020) which includes maintenance of the 'cold chain' and restriction of access to pharmacy and other authorised personnel.

25. The GM vaccine would be administered as an IM injection at vaccination centres. Following administration, all residual vaccine and associated waste which has come in to contact with the GM vaccine (such as syringes and swabs) will be discarded as clinical and related waste. Similarly, unused expired GM vaccine would be disposed of at vaccination or storage facilities in accordance with the relevant State and Territory legislation procedures for clinical/medical waste disposal methods such as

high temperature incineration. In addition, as part of the Australia's rollout for COVID-19 vaccinations, authorised vaccination providers must satisfy mandatory requirements established by the Australian government and complete compulsory online COVID-19 vaccination training, prior to being allowed to administer the vaccine.

Section 3 Parent organism

26. The GM vaccine is derived from human adenovirus serotype 26 (HAdV-D26). HAdV-D26 is a member of the genus *Mastadenovirus* in the *Adenoviridae* family. Adenoviruses (AdVs) are classified as Risk Group 2 microorganisms (Standards Australia/New Zealand, 2010). The characteristics of the parent organism provide a baseline for comparing the potential for harm from dealings with the GM vaccine. As such, the relevant biological properties of HAdVs will be discussed here.

27. Human adenoviruses (HAdVs) are categorised into seven species A to G based on their serology, sequence homology, serum neutralisation, hemagglutinin properties and genomic sequence (Ismail et al., 2018; Lange et al., 2019; Bots and Hoeben, 2020). HAdV-D26 belongs to species D, which is the largest species of adenoviruses (Mennechet et al., 2019).

28. Several HAdV species D viruses (HAdV-D) have been suggested as vaccine candidates, but to date HAdV-D26 is the best characterised in the group and has been evaluated in large-scale human vaccination trials (Mennechet et al., 2019) against Human Immunodeficiency Virus (HIV) (Baden et al., 2013; Barouch et al., 2013; Baden et al., 2015; Baden et al., 2020), Respiratory Syncytial Virus (RSV) (Sadoff et al., 2020a; Williams et al., 2020; Sadoff et al., 2021a) and Ebola (Pollard et al., 2020).

3.1 Pathology

29. HAdVs are common human pathogens and cause a wide range of illnesses such as common cold; sore throat; bronchitis; pneumonia; diarrhoea; conjunctivitis; fever; inflammation of the stomach, intestine and bladder; and neurologic disease (conditions that affect the brain and spinal cord) (Public Health Agency of Canada, 2014; CDC, 2019a).

30. HAdV infections are generally mild and self-limiting, but could be more severe or lethal in immunocompromised individuals (Mennechet et al., 2019). Overall, HAdV infections are responsible for about 2-5% of all respiratory infections in humans (Allard and Vantarakis, 2017) and is the most common cause of conjunctivitis in the world (Pihos, 2013).

31. Outbreaks of HAdVs-associated respiratory disease are more common in the late winter, spring and early summer, however infections can occur throughout the year. After natural HAdV infection, the incubation period of HAdVs ranges from 2 days to 2 weeks, depending on the viral species and serotype as well as the mechanism of acquisition (Public Health Agency of Canada, 2014; Allard and Vantarakis, 2017). For respiratory infections, the incubation period is generally 4-8 days, whereas it is 3-10 days for intestinal infections (Allard and Vantarakis, 2017). The symptoms of mild infection usually last for a few days to a week but for the severe infections, symptoms may last longer.

32. HAdV-D have been mainly associated with epidemic keratoconjunctivitis (EKC), which is endemic, but not isolated to Japan (Aoki and Tagawa, 2002). Serotypes that commonly associate with EKC are HAdV-D8, -D37, -D64, -D53, -D54 and -D56 (Kaneko et al., 2009; Walsh et al., 2009; Huang et al., 2014; Matsuura et al., 2019). Opportunistic HAdV infections in patients with HIV were also commonly from species D, and is associated with prolonged shedding in the gastrointestinal (GI) tract in these patients (Al Qurashi et al., 2012). There has been a single reported case where, a species D adenovirus (HAdV-D56) has been implicated in a neonatal fatality (Robinson et al., 2011b).

33. Like other HAdV-Ds, HAdV-D26 can also cause EKC (Baker et al., 2019). Experimental infections of human volunteers with HAdV-D26 through intranasal or conjunctival swabs resulted in very mild respiratory and eye infections and did not cause systemic disease (Knight et al., 1962; Lichtenstein and Wold, 2004a). Eye infections cause by HAdV-D26 were was self-limiting, mild to moderate in severity,

limited to the eye and rarely required medical intervention (Knight et al., 1962; Lichtenstein and Wold, 2004a). There was one reported case implicating HAdV-D26 infection as the cause of acute meningoencephalitis in an immunocompromised patient with a severe brain tumour and irradiation history (Dubberke et al., 2006).

3.2 Structure and genomic organisation

34. AdVs are non-enveloped, double-stranded DNA viruses with an icosahedral capsid comprising of major (hexon, penton base and fiber) and minor (protein IX, VIII, IIIa and VI) proteins; other proteins (V, VII, μ, Iva2, terminal protein and adenovirus protease); and a core that contains DNA (Robinson et al., 2011a; Yu et al., 2017). The genome of AdVs has approximately 30-35 kilobases (kb) which includes 30-40 genes (Lasaro and Ertl, 2009; Charman et al., 2019). The genome is flanked by inverted terminal repeats (ITRs).

35. The HAdV genome contains early and late genes, which are organised into transcription units (Figure 2). Early genes/regions (E1, E2, E3 and E4) are involved in directly activating transcription of other viral regions, altering the host cellular environment to enhance viral replication, and co-ordination of viral DNA replication (Roy et al., 2004; Lasaro and Ertl, 2009; Afkhami et al., 2016; Saha and Parks, 2017). The late genes (L1 to L5) encode components of the viral shell and other proteins that are involved in assembly of the capsid and are essential for production of new virus particles.

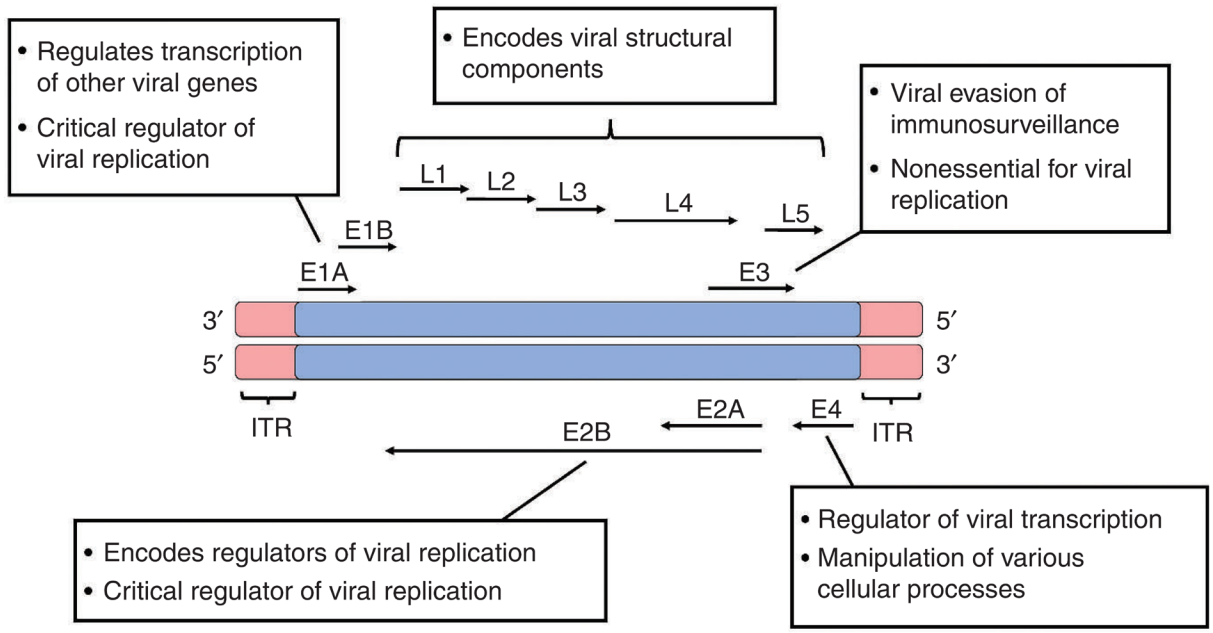

Figure 2: Functions, organisation and structure of adenovirus genome (Afkhami et al., 2016).

36. The E1 gene is composed of E1A and E1B. The E1A gene controls transcription of viral genes and redirects host-cell gene expression machinery to enable virus replication. The proteins produced from the E1A genes are the first proteins expressed from the infecting virus, and are essential for the efficient expression of other viral genes (Roy et al., 2004; Saha and Parks, 2017). The E1B gene assists in viral replication and is mainly required for the export of viral late mRNA (L1 to L5) from the host-cell nucleus into the cytoplasm. Together the E1A and E1B coding regions are essential for viral gene expression and replication (Roy et al., 2004; Saha and Parks, 2017).

37. The E2 gene is sub-divided into E2A and E2B that encode E2 proteins which are mainly involved in viral DNA replication and transcription of late genes (Roy et al., 2004; Saha and Parks, 2017). The E3 gene encodes viral proteins that aid the virus in evading the host immune response. The E4 gene modulates cellular function and assists with viral DNA replication and RNA processing.

3.3 Viral infection and replication

38. AdVs can infect a wide range of cells and tissues and replicate efficiently in both dividing and non-dividing cells. AdVs most frequently infect epithelia of the upper or lower respiratory tract, eyes, gastrointestinal and urinary tract tissues.

39. HAdVs uses the Coxsackie-adenovirus receptor (CAR) transmembrane proteins, CD46, CD80, CD86 and sialic acid to enter the host cells (Zhang and Bergelson, 2005; Lion, 2019). HAdV species C and E use the Coxsackie-adenovirus receptor (CAR) transmembrane proteins as the main receptor to gain entry to a variety of different cell types (Zhang and Bergelson, 2005; Lasaro and Ertl, 2009; Morris et al., 2016; Bots and Hoeben, 2020). HAdV-D26 also uses the CAR protein for entry but the affinity of this interaction is reduced compared to the classical HAdV-C5 (Baker et al., 2019). Instead, HAdV-D26 has been shown to use sialic acid-bearing glycans as a primary entry receptor (Baker et al., 2019).

40. The replication of AdVs takes place in the nucleus of the host cell and uses the host cell nuclear machinery to make copies of itself (Figure 3). Briefly, the AdV attaches to the receptors present on the cell membrane leading to internalisation of the virus by endosomal uptake. The virus is then uncoated resulting in the release of viral particles. The viral genome is transported into the nucleus where the transcription occurs (described above in para 36 and 37; (Charman et al., 2019). The viral DNA replication occurs in the nucleus before transport into the cytoplasm where viral structural proteins are made. The new virus particles are then assembled. Finally, the host cell breaks apart releasing the viruses (Waye and Sing, 2010b). Progeny viruses released from infected cells usually do not spread further than the regional lymph nodes.

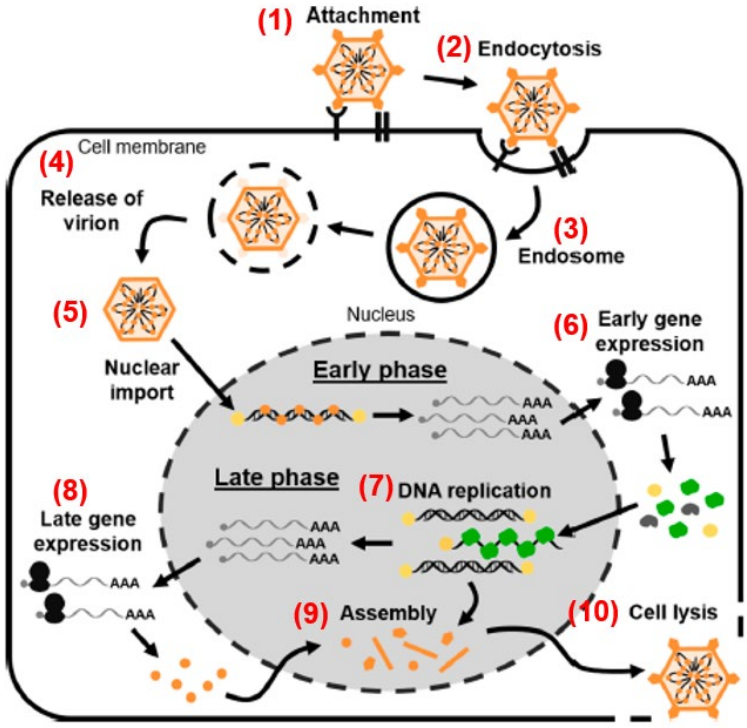

Figure 3: Overview of the adenovirus replication cycle (Charman et al., 2019).

3.4 Mutation and recombination of adenovirus

41. AdV DNA is maintained as multiple episomal copies in the cytoplasm of infected cells (Harui et al., 1999). In addition, AdVs do not have the machinery for efficient integration into the host genome and therefore AdVs exhibit extremely low levels of integration i.e., integration is a rare event (Harui et al., 1999; Desfarges and Ciuffi, 2012; Hoppe et al., 2015; Dehghan et al., 2019). However, random

integration of virus DNA into the host genome has been observed in very rare cases (Harui et al., 1999; Stephen et al., 2008).

42. Where a cell is infected by multiple AdVs at the same time, exchange of genetic material can occur, which promotes the molecular evolution of AdVs through a process called homologous recombination. Homologous recombination appears to be restricted to members of the same species and occurs in the regions of high sequence homology (Lukashev et al., 2008). However, bioinformatic analysis suggested that HAdV-E4, a species E adenovirus was a result of a recombination event between species B and C (Gruber et al., 1993).

43. HAdV-D genomes have one of the highest GC content among HAdV species, where GC content is associated with genome stability and resistance to recombination (Robinson et al., 2013). However, there are regions with reduced GC content that are prone to recombination (Robinson et al., 2013). Bioinformatic analysis have suggested that these regions are located at the hypervariable regions of the hexon, penton base, fiber and the E3 transcription unit (Robinson et al., 2011a; Robinson et al., 2013; Singh et al., 2013). The hexon protein is a major constituent of the viral capsid and is suggested to be critical for the development of adenovirus vaccines by forming the serum neutralisation epitope; the penton and fibre proteins are responsible for host cell binding and internalisation; and the E3 proteins facilitate immune evasion by the virus (Robinson et al., 2011a; Ismail et al., 2018). Homologous recombination in these regions could potentially alter the cell tropism of the virus and its ability to evade the immune system.

3.5 Epidemiology

3.5.1 Host range and transmissibility

44. Humans are the natural host for HAdVs (Custers, 2020). Experimentally, mice, cotton rats and rabbits have been infected with HAdVs to study adenovirus-induced disease (Ismail et al., 2019). Although used in animal models, HAdVs are unable to replicate in these animal models (Ismail et al., 2019) and no natural infections of non-human hosts have currently been described.

45. Transmission of HAdVs from an infected individual is primarily via direct contact with conjunctival secretions, inhalation of aerosols or the faecal-oral route (Allard and Vantarakis, 2017; Gray and Erdman, 2018; Khanal et al., 2018; CDC, 2019b). The virus can also be spread indirectly via contact with infected articles e.g. handkerchiefs, linens or utensils contaminated by respiratory discharge from an infected person (Allard and Vantarakis, 2017).

3.5.2 Bio-distribution and shedding

46. The predominant natural tropism of HAdV-D26 is ocular (eye) and gastrointestinal (gut) (Mennechet et al., 2019). Following natural HAdV infection, virus particles are shed via respiratory or ocular secretions or in the faeces. Respiratory infections generate the highest viral load early post-infection with residual virus remaining for up to 2 months post-infection (Huh et al., 2019). The ease of transmission of HAdV is thought to be facilitated by very high levels of viral particles shed into sputum or oral secretions of the infected person (Allard and Vantarakis, 2017).

47. HAdV shedding was also evaluated in faecal and oral swabs after oral administration of a live vaccine containing two HAdV serotypes (HAdV-E4 and HAdV-B7). Over 50% of the vaccine recipients tested positive for AdV faecal shedding between 7-28 days following vaccination. No faecal shedding was detected after 28 days following vaccination or at any time point in throat swabs (Allard and Vantarakis, 2017).

3.5.3 Prevalence

48. An estimation of the seroprevalance of HAdV-E4, -C5, -D26 and -B35 (serotypes commonly tested in the clinics or used in clinical/pre-clinical trials) is shown in Figure 4. This data is analysed based on approximately 30 studies published over the past 20 years (Mennechet et al., 2019). HAdV-E5 is the most

widely reported and has the highest seroprevalance globally. HAdV-D26, appears to have high seroprevalence in Africa and Asia; and low in North America and Europe (Mennechet et al., 2019).

49. In Australia, the Laboratory Virology and Serology (LabVISE) reports from the Department of Health (1991-2000) showed an average of about 1400 reported cases of adenovirus infection per year over 10 years and only about 18 reported cases of HAdV-D26 infection (Spencer, 2002). It is important to note that majority of adenovirus reported infection have not been serotyped and that testing for adenovirus infections may not be common in Australia. However, these numbers may indicate low prevalence of adenovirus infections in Australia.

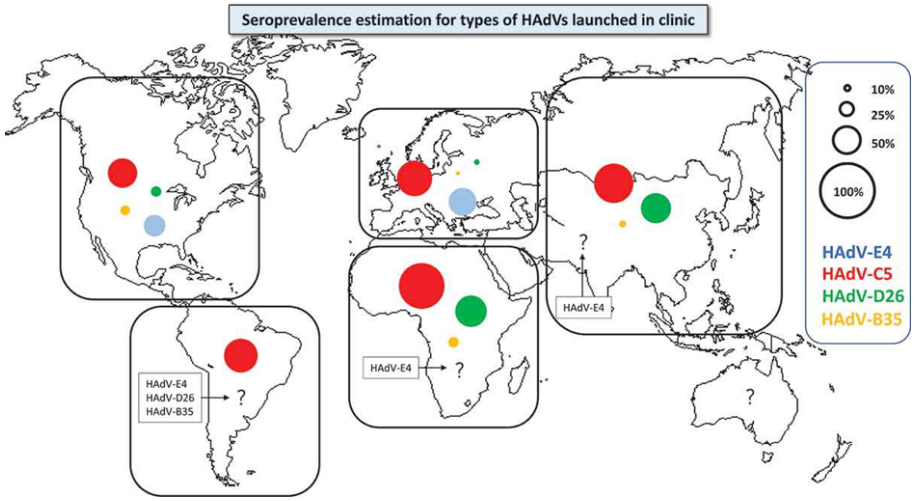

Figure 4: Seroprevalance for adenovirus types used in the clinic (Mennechet et al., 2019)

3.5.4 Control, environmental stability and decontamination methods

50. Infection with HAdV is generally asymptomatic or associated with mild disease in healthy adults and is generally managed through a combination of supportive care and enhanced personal hygiene measures to limit transmission. Antiviral drugs may be used in immunocompromised patients or those with severe disease. Antiviral agents such as Cidofovir and Ribavarin are commonly used as first line adenoviral therapies (Waye and Sing, 2010a; CDC, 2019a; Lion, 2019).

51. Despite the high prevalence of HAdV infection, there are currently no adenovirus-specific drugs to treat the infection (Waye and Sing, 2010a; CDC, 2019a). However, it has been suggested that sialic-acid binding inhibitors, such as Zanamivir, or trivalent sialic acid derivatives may make effective anti-HAdV-D26 therapies as it would block the primary entry receptor for HAdV-D26 (Baker et al., 2019).

52. AdVs are resistant to most chemical or physical decontamination processes and agents (including lipid-disrupting disinfectants) as well as high or low pH conditions (Rutala et al., 2006; Public Health Agency of Canada, 2014; Gray and Erdman, 2018). AdVs are also found to be resistant to UV radiation (Thompson et al., 2003; Thurston-Enriquez et al., 2003), thus supporting survival in treated wastewater and sewage, river, ocean and swimming pool water as well as drinking water (Public Health Agency of Canada, 2014).

53. AdVs are very stable in the environment at pH 6-8 and below 40˚C (Rexroad et al., 2006) and can survive for long periods in liquid or on surfaces in a desiccated state. For example, HAdV can survive up to 10 days on paper under ambient conditions and for 3-8 weeks on environmental surfaces at room temperature (Public Health Agency of Canada, 2014). Therefore, AdVs survival time depends on the relative humidity, temperature and on the type of surface (Abad et al., 1994).

54. HAdVs have been detected in various waters worldwide including wastewater, river water, drinking water, ocean and swimming pools (Allard and Vantarakis, 2017). HAdVs are more frequently detected in high concentrations in domestic sewage and sludge in various countries and in some situations may be used in surveillance for faecal contamination (Allard and Vantarakis, 2017).

55. AdVs are found to be sensitive to 70% ethanol, 0.9% Virkon S (>5 min contact time), 0.2% chlorine, 0.55% ortho-phthalaldehyde and 2.4% glutaraldehyde (McCormick and Maheshwari, 2004; Rutala et al., 2006). In addition, AdVs can be inactivated by heat e.g. heating to 56°C for 30 minutes or 60°C for 2 minutes or autoclaving (Public Health Agency of Canada, 2014; Allard and Vantarakis, 2017; Gray and Erdman, 2018).

Section 4 The GM vaccine - nature and effect of the genetic modification

56. The GM vaccine consists of a replication defective HAdV-D26 vector that has been genetically modified to produce a modified SARS-CoV-2 spike glycoprotein. The GM vaccine is designed to provide protection from infection with SARS-CoV-2 which causes COVID-19 disease.

4.1 The genetic modifications

57. The HAdV-D26 vector was produced using standard molecular cloning techniques, where the E1 and E3 genes are deleted from the HAdV-D26 genome; and the E4 open reading frame (*orf6*) is replaced with equivalent genes from HAdV-C5 into the same locus (Abbink et al., 2007; Bos et al., 2020). To produce the GM vaccine, a mammalian expression cassette containing a human cytomegalovirus (CMV) promoter, tetracycline operator (TetO) sites, a simian virus 40 (SV40) polyadenylation signal and a gene encoding a modified full length SARS-CoV-2 spike protein (S protein) (GenBank accession number MN908947) was inserted into the E1 locus of the HAdV-D26 vector (Bos et al., 2020).

58. The S protein is comprised of the receptor binding (S1) and membrane fusion (S2) subunits. The S1 receptor binding domain has been shown to be responsible for host range and tropism (Huang et al., 2016; Li, 2016; Letko et al., 2020; Mousavizadeh and Ghasemi, 2020; Samrat et al., 2020). The S1 subunit facilitates the virus attachment via angiotensin-converting enzyme 2 (ACE2) receptors present on human cells and subsequent fusion of virus and cell membranes, mediating the entry of SARS-CoV-2 into the target host cells. The fusion of the S protein to the host cell membrane is mediated by cleavage of the S protein by host cell proteases, the transmembrane protease/serine subfamily member 2 (TMPRSS2) and furin at specific cleavage sites at the S2' or between the S1 and S2 subunits respectively (Sternberg and Naujokat, 2020). Modifications have been made to the genetic sequence of the S protein in this GMO at specific protease cleavage sites to stabilise the S protein in its pre-fusion state (Bos et al., 2020; Sternberg and Naujokat, 2020).

59. The roles of the SARS-CoV-2 S protein in receptor binding and entry into the host cells make it an attractive vaccine candidate and many developing COVID-19 vaccines have been designed based on it (Bos et al., 2020; Folegatti et al., 2020; Logunov et al., 2020; Sadoff et al., 2020b; Samrat et al., 2020; Zhu et al., 2020).

4.2 Effect of the genetic modification

60. The deletion of E1 and E3 genes in the GMO removes its capacity to replicate in cells and evade the host immune response.

61. The modification of the E4 gene allows efficient expression and growth of the virus in human cells during manufacturing of the GM vaccine and hence increases the yield of the GMO during production.

62. The S protein inserted as a transgene allows the GMO to produce the S protein once it infects human cells. This would then induce an immune response in the host towards the S protein and build an immunity towards SARS-CoV-2.The insertion of the S protein does not interfere with the backbone of the vector or contribute to the generation of replication competent virus. The S protein is also not involved

in the formation or the composition of the capsid of the HAdV-D26 vector and therefore is not considered to affect the tropism and host range of the vector.

63. As a result of these genetic modification, the GMO cannot replicate in the host cells and will induce an immune response in humans but will not cause ill-health.

4.3 Characterisation of the GMO

64. Data obtained from pre-clinical and clinical trials using the proposed GMO and from other clinical trials using the same backbone/platform (HAdV-D26 vector) with different genes for a range of diseases has been used to describe the characteristics of the GMO.

4.3.1 Genetic stability and molecular characterisation

65. The HAdV-D26 vector, as adenoviruses in general is considered to be genetically stable (Vujadinovic et al., 2018). Due to the lack of sequence overlap between HAdV-D26 vector and cell lines used during the manufacturing process, the incidence of the formation of replication-competent adenovirus (RCA) is very low. The GMO will be routinely monitored during manufacturing to ensure the virus has not gained replication competency. The result of RCA testing will be reported as "no RCA detected" if it complies with the criterion of <1 RCA/3 x 10^{10} viral particles (VP). This acceptance criterion is based on the Food and Drug Administration (FDA) guidance document and the FDA Biological Response Modifiers Advisory Committee (BRMAC) meeting number 30 (Adenovirus Titer Measurements and RCA levels; April 5, 2001).

66. The GM vaccine would also undergo identity polymerase chain reaction (ID-PCR) of the transgene and adenovirus specific regions against the reference identity standards to confirm HAdV-D26 vector identity. In addition, sodium dodecyl sulphate – polyacrylamide gel electrophoresis (SDS-PAGE), Western Blot and enzyme-linked immunosorbent assays (ELISA) are used to measure and confirm S protein expression. The amount of viral particles/vector concentration in the GM vaccine will be quantified using quantitative polymerase chain reaction (qPCR).

67. The GM vaccine does not contain a selectable marker, however the GMO can be distinguished from the HAdV-D26 (parent strain) or SARS-CoV-2 using a specific PCR test. These genetic markers allow the identification of the modified S protein sequence, the absence of E1 and E3 genes, and the modified E4 gene region. Thus, each vaccine batch will be subjected to a number of tests to ensure consistency and quality of the manufactured product.

68. AdV vectors are considered non-integrating vectors and do not have a tendency to integrate or reactivate in a host (EMEA, 2007; FDA, 2020). The viral DNA is maintained as multiple episomal copies in the infected nuclei. However, some studies in cell lines and mice have suggested plausible integration of AdV vectors into host genomes at very low frequencies (Hillgenberg et al., 2001; Stephen et al., 2010). A study on cell lines from human, hamster, monkey and mice calculated the integration frequency of approximately one in every 10^3 to 10^5 transduced cells (Harui et al., 1999). In a separate study on immunodeficient mice, intravenous administration of replication incompetent AdV vector showed plausible low integration of the AdV vector into the host genome (Stephen et al., 2010). However, the authors did acknowledge that the most common route of vector delivery for AdV vectors (i.e. IM route of injection) would result in much lower incidence of gene transfer (Stephen et al., 2010). No clinical or human studies have shown integration of AdV vectors into the host genome.

4.3.2 Bio-distribution and shedding of the GMO

69. No bio-distribution data is available for this GMO, however bio-distribution studies, using the same HAdV-D26 platform administered via IM injection, have been carried out in rabbits, with vaccines for HIV (Ad26.ENVA.01) and RSV (Ad26.RSV.preF) (Custers, 2020) (EMA, 2002). The vector DNA was primarily detected at the site of injection, draining lymph nodes and to a lesser extent the spleen. The amount of detectable vector DNA was shown to decrease with time post-inoculation and was below the limit of detection in all other tissues examined at each time points (Days 11, 61 and 91 for Ad26.ENVA.01; Days

11, 90, 120 and 180 for Ad26.RSV.preF). These data demonstrated that the HAdV-D26 vector has limited bio-distribution following IM injection and does not persist and/or replicate in tissues following vaccination. These results were consistent regardless of the transgene inserted.

70. A bio-distribution study involving HAdV-C5 and HAdV-B35 vectored vaccines after IM injection into rabbits showed similar bio-distribution results, and viral DNA was shown to be cleared within 3 months (Sheets et al., 2008). Together these data suggests that the bio-distribution of HAdV vectors are independent of the transgene and type of adenoviral vector used (HAdV-D26, HAdV-C5 and HAdV-B35). The GMO is likely to have a similar bio-distribution as other HAdV vectored vaccines.

71. No clinical shedding data is available for this GMO. However, studies targeting other diseases using the same HAdV-D26 vector via IM administration have not detected replication-competent adenovirus in oral swabs and urine specimens of patients at Day 14 post-administration or in tests conducted during subsequent illness suspected to be of viral origin (Baden et al., 2013; Baden et al., 2015). In addition, vector DNA was not detected in urine and nasal swabs at days 1, 2 and 9 post-inoculation using a similar HAdV-D26 vector expressing a different transgene (Pollard et al., 2020). Therefore, it is not expected that the S protein would impact the bio-distribution and shedding of the HAdV-D26 vector.

72. The inability of the GMO to replicate prevents its dissemination in the vaccinated person. Taken into consideration the above mentioned bio-distribution and shedding data from replication incompetent adenoviral based vaccines, the GMO is expected to be confined to the IM injection site and the draining lymph nodes of the human host and no virus excretion is expected with the GMO.

4.3.3 Stability in the environment and decontamination

73. The stability of this GMO in the environment (surfaces, water types and sediments) has not been tested. Other recombinant AdVs (AdV expressing GFP) have been shown to have reduced capacity to survive in fresh surface water, cold water and dark sediments compared to wild-type AdVs (Rigotto et al., 2011; Elmahdy et al., 2018). Since the GMO is unable to replicate, it is likely that it would have similar or reduced survival and persistence in the environment compared to the parent organism and would degrade over time (see Chapter 1, Section 3.5.4).

74. Methods of decontamination effective against the parent organism, HAdV-D26, are expected to be equally effective against the GMO (see Chapter 1, Section 3.5.4).

4.3.4 Non-clinical studies

75. Pre-clinical studies with the GM vaccine in mice, hamsters and rhesus macaques have shown a good safety profile; the ability to induce robust cellular and neutralising antibody responses with a single dose of the GM vaccine; and also resulted in protective efficacy against SARS-CoV-2 infection (Bos et al., 2020; Mercado et al., 2020; Tostanoski et al., 2020; van der Lubbe et al., 2021).

4.3.5 Safety and immunogenicity in clinical studies

76. Clinical phase I/IIa studies have been carried out as a single or double IM dose in two patient cohorts in the United States and Belgium (Cohort 1: age 18-55; 402 patients and Cohort 3: ≥65; 403 patients) using this GM vaccine (ClinicalTrials.gov; NCT04436276). Cohort 1 consisted of 162 patients that were given a low dose, 158 patients that were given the high dose and 82 in the placebo group. Cohort 3 consisted of 161 patients that were given low dose, 161 patients that were given the high dose and 81 in the placebo group. Interim published results from the study demonstrated a good safety profile after the first dose (Sadoff et al., 2020b; Sadoff et al., 2021b). Adverse events were mild or moderate, resolved within 1 to 2 days after vaccination and were less common in the older cohort (Sadoff et al., 2020b; Sadoff et al., 2021b). Most frequently reported adverse events were pain at the injection site, fatigue, headache, myalgia and fevers (Sadoff et al., 2020b; Sadoff et al., 2021b).

77. A single dose of the GM vaccine induced a strong neutralising antibody and robust T cell responses in both patient cohorts (older and younger) (Sadoff et al., 2020b; Sadoff et al., 2021b). Interim results also suggests that immune reaction to the vaccine dose (reactogenicity) was higher with a higher dose

and in the younger patient cohort compared to the cohort of older patients (Sadoff et al., 2020b; Sadoff et al., 2021b). Further information on the immunogenicity after the second dose would be published by the study sponsor when the data becomes available. Further phase III clinical trials are currently being carried out (United States, Argentina, Brazil, Belgium, Chile, Colombia, France, Germany, Mexico, Peru, Philippines, South Africa, Spain, United Kingdom) using the GM vaccine both as a single-dose (ClinicalTrials.gov; NCT04505722; estimated 60, 000 patients) and double dose (NCT04614948; estimated 30, 000 patients) studies.

Note: Clinical trials with the GMO are currently ongoing and the data taken from the published studies in this section represent an interim analysis, therefore, the safety and immunogenicity data from clinical studies might change once the studies are completed. The TGA would formally assess the patient safety and the quality and efficacy of the COVID-19 vaccine prior to its registration in the ARTG.

4.4 HAdV-D26 vector in other vaccine clinical trials

78. The same HAdV-D26 vector has been used in several other clinical trials for other human diseases, including the Ebola virus (ClinicalTrials.gov NCT02376426, NCT02376400, NCT02313077 and NCT02416453) (Milligan et al., 2016; Anywaine et al., 2019; Mutua et al., 2019; Pollard et al., 2020), Human immunodeficiency virus (HIV) (NCT01215149, NCT01103687, NCT00618605, NCT02685020, NCT02788045 and NCT02315703) (Barouch et al., 2013; Baden et al., 2015; Baden et al., 2016; Stephenson et al., 2018; Baden et al., 2020) and Respiratory Syncytial Virus (RSV) (NCT03339713) (Sadoff et al., 2020a; Sadoff et al., 2021a). Mostly, adverse events were mild or moderate in intensity in these studies. There are only two rare reported cases of probably vaccine related serious adverse events in these GM vaccine clinical trials, one each for Ebola (Pollard et al., 2020) and HIV (Baden et al., 2020). Overall, these GM vaccines are well tolerated, showed a good safety profile and are able to mount a good immune response.

79. A GM vaccine using the same HAdV-D26 vector was approved for Ebola by the European Commission in July 2020 (Zabdeno; Ad26.ZEBOV).

Section 5 The receiving environment

80. The receiving environment forms part of the context for assessing risks associated with dealings with GM vaccine (OGTR, 2013). It informs the consideration of potential exposure pathways, including the likelihood of the GMO spreading or persisting outside the site of release.

5.1 Site of vaccination

81. The intended primary receiving environment would be the muscles (at the site of injection) of the vaccine recipient as the GM vaccine will be delivered via an IM injection by a trained healthcare professional at vaccination centres.

82. The secondary receiving environment would be the clinical facility/vaccination centres where the vaccine is prepared and administered. Most vaccination facilities/centres would be equipped to deal with scheduled drugs and infectious agents. They typically comply with AS/AZS 2243.3:2010 Safety in laboratories – Microbiological Safety and Containment (Standards Australia/New Zealand 2010). Also, as mentioned in Section 2.1, facilities would need to comply with all aspects covered in the COVID-19 vaccination training delivered by The Australian Government in partnership with the Australian College of Nursing.

83. The principal route by which the GMO may enter the wider environment following vaccination is via shedding. However, as the administration of non-replicating GMO is via IM injection, wide spread shedding is not expected due to localisation of viral particles at the injection site and draining lymph nodes. Further, GMO may also enter the environment via accidental spills of unused vaccine.

5.2 Presence of related viral species in the receiving environment

84. The presence of related viruses may offer an opportunity for introduced genetic material to transfer between the GMO and other organisms in the receiving environment.

85. AdVs belong to five genera: *Aviadenoviruses* (infecting birds), *Mastadenovirus* (infecting mammals), *Atadenovirus* (infecting a broad range of hosts including reptiles, lizards and some mammals), *Siadenovirus* (infecting one species of frog and tortoise and multiple species of domestic, wild and captive birds) and *Ichtadenovirus* (infecting fish) (Tong et al., 2010; Lange et al., 2019; Vaz et al., 2020). As such, they are a common cause of infection in animals and humans of all ages and can be found in all environments where humans or animals congregate in groups (Usman and Suarez, 2020). A more detailed description of AdVs presence in the environment is in Section 3.5.4.

86. The prevalance of HAdVs in Australia based on the reported cases and seroprevalance is low as mentioned in Section 3.5.3.

87. Adenovirus-based vaccines or clinical trial treatments were previously used for other diseases. Therefore, similar adenovirus-based vectors could be present in people or the environment.

5.3 Presence of similar genetic material in the environment

88. The balance of a system could be perturbed by the introduction of new genetic material through horizontal gene transfer or through release of GMO into the environment. However, the effect of perturbation would be relatively small if the genetic material was already present in the system and did not confer any selective advantage to an organism that gained this genetic material.

89. All of the genes in the GMO would be functionally similar to ones present in the naturally occurring SARS-CoV-2 virus. The genes introduced into the GMO were derived from naturally occurring SARS-CoV-2 virus and so similar genetic material would already be present in the environment.

Section 6 Previous authorisations

90. This GM vaccine has not been previously authorised for commercial supply in any region or country.

91. There are currently 3 ongoing clinical trials (as mentioned in Section 4.3.5) to test the safety, immunogenicity, and efficacy of GM vaccine in different countries for the prevention of COVID-19.

92. The initial importation, transport, supply, storage and disposal of the GM vaccine stocks into Australia and dealings involving quality control sampling and batch release testing is covered under Notifiable low risk dealings (NLRDs) authorisation held by Janssen-Cilag.

93. The Regulator has not approved any licences in relation to this GM vaccine.

Chapter 2 Risk assessment

Section 1 Introduction

94. The risk assessment identifies and characterises risks to the health and safety of people or to the environment from dealings with GMOs, posed by or as the result of gene technology (Figure 4). Risks are identified within the established risk assessment context (Chapter 1), taking into account current scientific and technical knowledge. A consideration of uncertainty, in particular knowledge gaps, occurs throughout the risk assessment process.

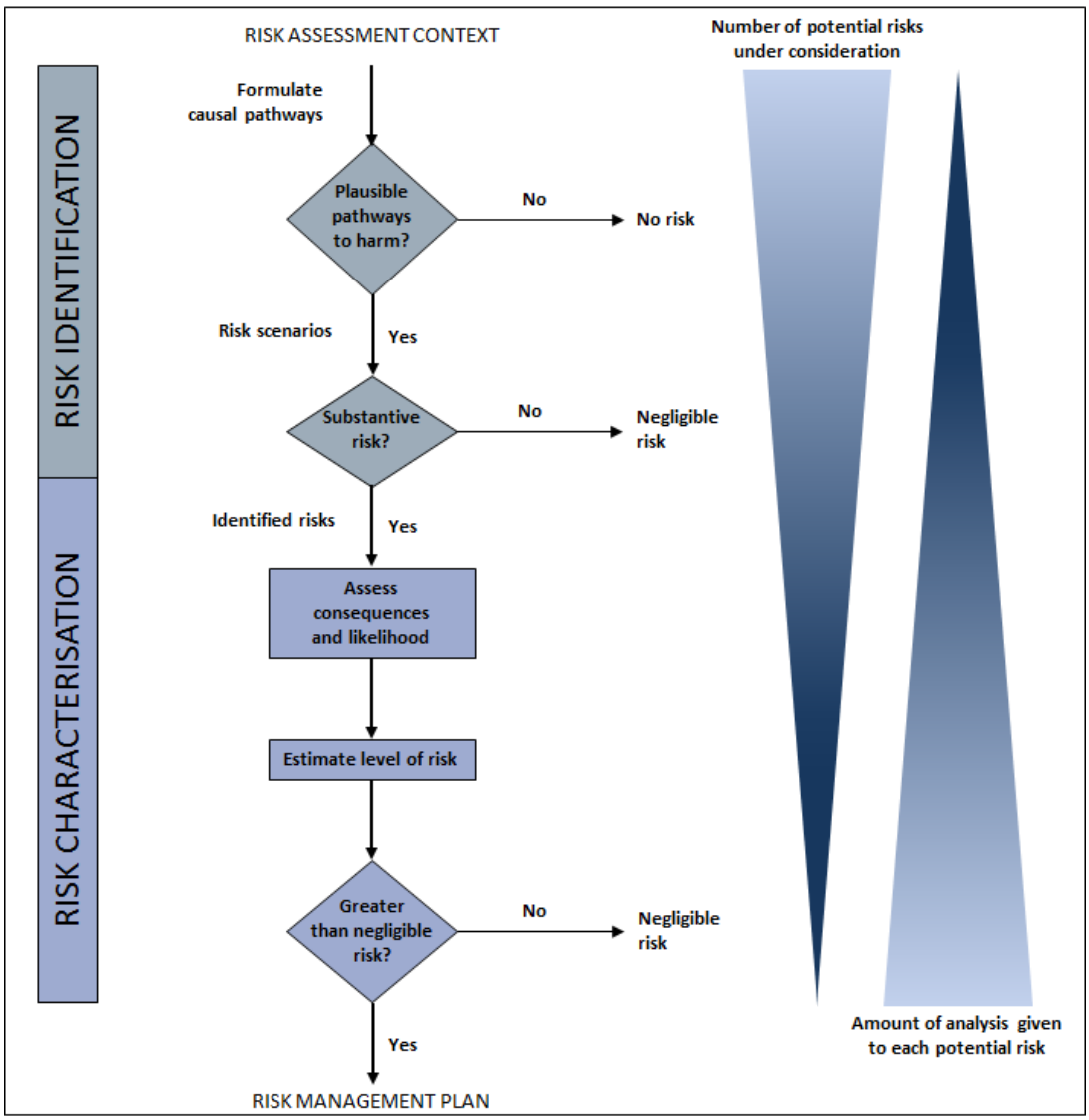

Figure 4: The risk assessment process

95. The Regulator uses a number of techniques to identify risks, including checklists, brainstorming, previous agency experience, reported international experience and consultation (OGTR, 2013).

96. Risk identification first considers a wide range of circumstances in which the GMO, or the introduced genetic material, could come into contact with people or the environment. This leads to postulating causal pathways that may give rise to harm for people or the environment from dealings with a GMO. These are called risk scenarios.

97. Risk scenarios are screened to identify substantive risks, which are risk scenarios that are considered to have some reasonable chance of causing harm. Risk scenarios that could not plausibly occur, or do not lead to harm in the short and long term, do not advance in the risk assessment process (Figure 4), i.e. the risk is considered no greater than negligible.

98. Risk scenarios identified as substantive risks are further characterised in terms of the potential seriousness of harm (Consequence assessment) and the likelihood of harm (Likelihood assessment). The consequence and likelihood assessments are combined to estimate the level of risk and determine whether risk treatment measures are required. The potential for interactions between risks is also considered.

Section 2 Risk identification

99. Postulated risk scenarios are comprised of three components (Figure 5):

i. The source of potential harm (risk source)

ii. A plausible causal linkage to potential harm (causal pathway), and

iii. Potential harm to people or the environment.

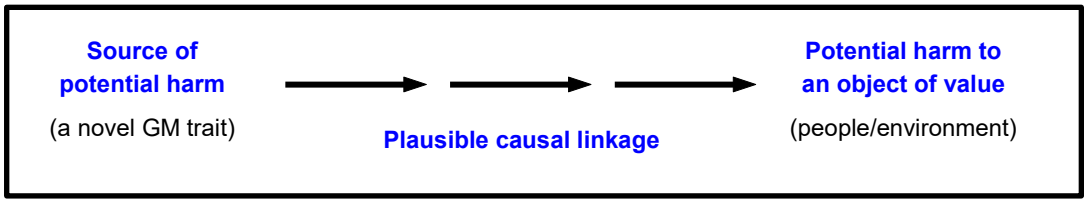

Figure 5: Components of a risk scenario

100. When postulating relevant risk scenarios, the risk context is taken into account, including the following factors detailed in Chapter 1:

- the proposed dealings
- the proposed limits including the extent and scale of the proposed dealings
- the proposed controls to limit the spread and persistence of the GMO and
- the characteristics of the parent organism(s).

2.1 Risk source

101. The parent organism is a human adenovirus serotype 26 (HAdV-D26). Details of the pathogenicity and transmissibility of HAdV is discussed in Chapter 1. Infection is generally the result of inhalation of aerosolised droplets excreted from respiratory or ocular secretions containing the virus or mucosal exposure to the virus or via faecal-oral transmission. HAdV infects humans and causes common cold-like symptoms, eye infections or diarrhoea.

102. Infection with AdV could result in latent infection in lymphoid tissues and increase the period of viral persistence in the body. However, the AdV remains episomal throughout the infection and does not integrate into the host DNA as discussed in Chapter 1, Section 4.3.1. Thus, the consequences of integration of viral DNA into a host cell genome will not be further discussed.

103. Toxicity and allergenicity of the introduced genes and their protein products have not been directly considered, but are taken into account in the context of their contribution to ill health.

104. Potential sources of harm can be due to the intended novel GM traits associated with one or more introduced genetic elements, or unintended effects/traits arising from the use of gene technology. Unintended effects can arise through horizontal gene transfer (HGT) which is the stable transfer of genetic material from one organism to another without sexual reproduction. All genes within an organism, including those introduced by gene technology, can be transferred to another

organism by HGT. A gene transferred through HGT could confer a novel trait to the recipient organism. The novel trait may result in negative, neutral or positive effects on the fitness of the recipient organism. HGT commonly occurs from cells to viruses but rarely occurs from viruses to their host cells, with the exception of retroviruses and some DNA viruses. This pathway is further considered as a potential source of risk.

105. As discussed in Chapter 1, Section 4.1, the GMO has been modified by the deletion of the E1 and E3 genes, by modifying the E4 gene and by insertion of a gene encoding a modified SARS-CoV-2 spike protein. These introduced genes and their encoded proteins are considered further as a potential source of risk.

2.2 Causal pathway

106. The following factors are taken into account when postulating plausible causal pathways to potential harm:

- the proposed dealings, which are import, transport or disposal of the GMO and possession (including storage) in the course of any of these dealings,
- restrictions placed on the import, transport or disposal of the GMO by other regulatory agencies, the States and Territories,
- characteristics of the parent organism,
- routes of exposure to the GMOs, the introduced gene(s) and gene product(s),
- potential effects of the introduced gene(s) and gene product(s) on the properties of the organism,
- potential exposure of other organisms to the introduced gene(s) and gene product(s) from other sources in the environment,
- potential exposure of other organisms to the GMOs in the environment,
- the release environment,
- spread and persistence of the GMOs (e.g. dispersal pathways and establishment potential),
- environmental stability of the organism (tolerance to temperature, UV irradiation and humidity),
- gene transfer by horizontal gene transfer,
- unauthorised activities, and
- practices before and after administration of the GMO.

107. The TGA regulate quality, safety and efficacy of the GM vaccine (i.e., GMO) under the *Therapeutic Goods Act 1989*, as mentioned in Chapter 1, Section 1.1. This includes:

- assessment of patient safety, vaccine quality and efficacy prior to inclusion on the ARTG,
- recommended practices for the transport, storage and disposal of the GM vaccine under the *Australian code of good wholesaling practice for medicines in schedules 2, 3, 4 & 8,*
- requirements for the scheduling, labelling and packaging under the *Poisons Standard.*

108. The current assessment focuses on risks posed to people other than the intended vaccine recipient, and to the environment, including long term persistence of the GMOs, which may arise from the import, transport, storage or disposal of the GMO.

109. The Act provides for substantial penalties for unauthorised dealings with GMOs or non-compliance with licence conditions, and also requires the Regulator to have regard to the suitability of an applicant to hold a licence prior to the issuing of the licence. These legislative provisions are considered sufficient to minimise risks from unauthorised activities. Therefore, unauthorised activities will not be considered further.

110. As discussed in Chapter 1, Section 4.3.2, the HAdV-based viral vectors were found to be localised to the site of injection and draining lymph nodes after IM injection. Further, no viral shedding was detected with HAdV-based viral vectors. Therefore, the GMO is expected to be confined to the IM injection site and the draining lymph nodes of the vaccine recipients and not expected to shed from vaccine recipients into the environment. Thus, the risk of the GMO being released into the environment from viral shedding after vaccine administration will not be considered further.

111. As mentioned in Chapter 1, Section 3.4, adenoviruses remain episomal throughout the infection and do not integrate into the host DNA. Similarly, the vectors derived from these adenoviruses are considered as non-integrating vectors which do not have a propensity to integrate or reactivate following latency in a host (EMEA, 2007; FDA, 2020). Further, adenoviral vectors (including HAdV-26 vector) have been used extensively in clinical studies as a vaccine and gene therapy for almost 30 years (Crystal, 2014) and there is no evidence of integration of viral DNA into the host genome. Thus, the consequences of integration of viral DNA into a host cell genome will not be further discussed.

2.3 Potential harms

112. The following factors are taken into account when postulating relevant risk scenarios for this licence application:

- harm to the health of people or desirable organisms, including disease in humans or animals or adverse immune response to the GMO
- the potential for establishment of a novel virus that could cause harm to people or the environment

2.4 Postulated risk scenarios

113. Three risk scenarios were postulated and screened to identify substantive risk. These hypothetical scenarios are summarised in Table 1 and discussed in depth in sections 2.4.1-2.4.3 (this chapter).

114. In the context of the activities proposed by the applicant and considering both the short and long term, none of the three risk scenarios gave rise to any substantive risks that could be greater than negligible.

Table 1 Summary of hypothetical risk scenarios from dealings with GM vaccine

Risk scenario	Risk source	Possible causal pathway	Potential harm	Substantive risk	Reason
1	GMO	Exposure of other people and animals to the GMO via needle-stick injury, aerosols, fomites, contact with abraded skin or mucous membranes during (a) Preparation and administration of the GMO (b) Import, transport or storage of the GMO (c) Disposal of the GMO ⬇	Adverse immune reactions (e.g., cytokine storm)	No	• The GMO is replication incompetent. GMO will not produce further viral particles to sustain an infection. • Any reactions to the spike protein would be transient and the GMO would be rapidly cleared by the immune system. • GMO has shown good safety profile. • The dose received through accidental exposure would

Risk scenario	Risk source	Possible causal pathway	Potential harm	Substantive risk	Reason
		Transduction of cells by GMO ⬇ Expression of the spike protein			be far smaller than that administered during vaccination and would not be sufficient to induce an adverse immune response. • Import, transport, storage and disposal will follow well established procedures.
2	GMO	Exposure of other people and animals to the GMO as mentioned in Risk Scenario 1 ⬇ Transduction of cells by GMO ⬇ Transduced cells co-infected with AdV ⬇ (a) Complementation of E1 and E3 by AdV (b) Homologous recombination with AdV ⬇ Production of other recombinant GMOs as described in Table 2	Adverse immune reactions (e.g., cytokine storm) Disease in people or animals	No	• There is a low probability of both GMO and AdV infecting the same cell at the same time. • There is a low probability of continuous complementation of GMO by AdV because AdV infection is self-limiting. • Low reported HAdV infection rates in Australia. • Recombination among adenoviruses is restricted to the same species and are very rare events. • Homologous recombination could occur in regions with high homology, which are involved in virus tropism (capsid proteins) or immune-evasion (E3). Recombination at E1 is less likely to occur. • Multiple recombinations are required to produce a replication competent HAdV with altered tropism and immune evasion properties.
3	GMO	GMO release into the environment (e.g. sewerage, spills) ⬇ Exposure to people or animals ⬇ As per scenario 1-2	Adverse immune reactions (e.g. cytokine storm); Disease in people or animals	No	• As discussed in Risk Scenario 1 and 2. • GMO does not infect aquatic species. GMO cannot persist and replicate inside or outside the host, hence GMO is unable to maintain a stable presence in the environment for long periods.

2.4.1 Risk scenario 1

Risk source	GMO
Causal pathway	Exposure of other people and animals to the GMO via needle-stick injury, aerosols, fomites, contact with abraded skin or mucous membranes during (a) Preparation and administration of the GMO (b) Import, transport or storage of the GMO (c) Disposal of the GMO ⬇ Transduction of cells by GMO ⬇ Expression of the spike protein
Potential harm	Adverse immune reactions (e.g., cytokine storm)

Risk source

115. The source of potential harm for this postulated risk scenario is the GMO.

Causal Pathway

116. People (person handling the GMO) and animals could be directly or indirectly exposed to the GMO in a number of ways. The GMO could be transmitted via aerosol droplets generated during an unintentional spill of the GMO and preparation of the GMO. It could also be transmitted when contaminated surfaces, such as hands or tissues, make contact with mucous membrane or via needle stick injury. This exposure could result in infection with the GMO that could lead to ill health.

Exposure during preparation and administration of the GMO

117. As discussed in Chapter 1, Section 2.1, the GMO would be distributed via vaccination clinics/centres. There is the potential for exposure of people involved in the administration of the GM vaccine by needle stick/sharps injury, aerosols formation during preparation and/or due to breakage/spillage of GM vaccine onto surfaces during preparation and administration.

118. The GMO would be prepared and administered by authorised, experienced and trained health professionals. All personnel working in settings where healthcare is provided, including vaccination services, are required to comply with the standard precautions for working with potentially infectious material, as described in the *Australian Guidelines for the Prevention and Control of Infection in Healthcare* (2019), *the Australian Immunisation Handbook* and the Australian Government's COVID-19 vaccination training program. Compliance with these behavioural practices at vaccination centres will limit and control unintended exposure of people to the GMO.

119. Caregivers and healthcare personnel who come into close contact with vaccinated people may be inadvertently exposed to the GMO during administration via accidental needle stick injuries or spillage. Caregivers and others exposed to the GM vaccine in this way would only be expected to be exposed to low levels of the GMO and this is not expected to result in any negative effects or ill-health. Furthermore, formation of replication-competent adenovirus or presence of the vector in healthcare personnel who came into close contact with patients have not been observed in studies which looked into these parameters (Schenk-Braat et al., 2007).

120. The existing work practices mentioned above would minimise the potential exposure of people to the GMOs during administration of the vaccine.

Exposure during import, transport and storage of the GMO

121. If the GM vaccine was unintentionally/accidentally spilled or lost during import, transport or storage, this could result in exposure to people or animals in the area via aerosol or liquid contact

with eyes or mucous membranes/skin. Further, people or animals could be inadvertently exposed to the GMO via contact with materials or surfaces contaminated with the GMO through subsequent hand to mouth transmission. This could result in infection with the GMO.

122. The applicant proposes to import the GMO from overseas as a multi-dose vial. These vials would be packaged in secondary cartons and the cartons packed in shipping cartons for distribution (Chapter 1, Section 2.1). Transport of GMO between the port of entry and the warehouse would continue in this packaging. This would lower the likelihood of unintended dispersal of the GMOs.

123. Vaccines are classified as Schedule 4 medicines. Therefore, storage, handling and transport would be in accordance with *the Australian code of good wholesaling practice for medicines in schedules 2, 3, 4 & 8 (TGA, 2011) and the WHO's Good Distribution Practices for pharmaceutical products (WHO, 2010)*. These practices would minimise the chances of damaged and leaking stock going unnoticed and increase the chances of GM vaccine being handled by individuals who would know how to decontaminate a spill, thus minimising the probability of unintended dispersal of the GMOs.

124. Additionally, the GM vaccine would be transported and stored according to the *National Vaccine Storage Guidelines: Strive for 5* (Department of Health, 2019) and *the Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP, 2020). The cold chain, which is intended to preserve the potency of the vaccine, requires cold packaging/ refrigeration and this adds a level of containment during import, storage and transport.

125. The risk of exposure to the GMO resulting in disease in other people and animals is negligible because the GMO is replication incompetent. Further, the presence of animals during import, transport and storage is highly unlikely unless the spill occurs outside the premises/shipping containers.

126. Decontamination agents and methods, suitable for adenoviral vectors would be used in accordance with local requirements and legislation, for decontamination and disinfection measures after administration of the vaccine or in the case of accidental spills during the commercial supply of the vaccine.

127. The import, transport and storage procedures discussed above meet the requirements of the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs* and would mitigate exposure due to spills of the GMO during these dealings.

Exposure during disposal of the GMO

128. Individuals may be inadvertently exposed to GMOs while disposing of used, expired, or unused vials of the GM vaccine. The two locations where this is most likely to occur are at:

- distribution warehouses where stocks of the GM vaccine are held;
- locations where the GM vaccine is administered.

129. The *Australian code of good wholesaling practice for medicines in schedules 2, 3, 4 & 8* (TGA, 2011) requires:

- specific training for personnel handling medicines that pose high risk to personnel if package integrity is breached or spillage occurs ;
- waste medicines be collected and destroyed by a person who is licensed or permitted to do so under relevant State or Territory legislation;
- medicines for destruction be enclosed in sealed packaging or in a container.

130. As discussed in Chapter 1, Section 2.1, unused and expired vials of the GMO as well as the vials with residual GMO, syringes and waste contaminated with the GMO would be treated as clinical/medical waste and disposed of in accordance with the waste disposal methods approved by

the Environmental Protection Agency or Health Department in the relevant State or Territory (TAS, 2007; NT, 2014; WA, 2016; ACT, 2017; NSW, 2018; QLD, 2019; SA, 2020; VIC, 2020). Adherence with these procedures would reduce the likelihood of accidental exposure of people or animals to the GMO.

131. For a productive infection to occur, individuals must be exposed to an infectious dose. Residual liquid in used vials and used syringes would not contain a sufficient titre to cause a productive infection. The same would apply to secondary waste such as gloves that may be contaminated with the GMO. The GMO is unable to replicate inside and outside the host, so viruses in the used vials could not multiply to reach an infective dose. Thus, the dose received through accidental exposure would be far smaller than that administered during vaccination. Therefore, even if an individual or animal is inadvertently exposed to the GMOs, they are unlikely to develop disease.

132. Taken together, the disposal and decontamination procedures discussed above would minimise likelihood of exposure that could be associated with conducting these dealings with the GMOs.

Potential harm

133. If people or animals are exposed to the GMOs, they could develop flu-like symptoms, eye infections or local inflammation for a short period of time before the virus is cleared by the immune system. It is plausible that exposed people or animals could experience an adverse immune response or disease.

134. As the GMO is replication incompetent, it is unable to produce further viral particles which are required to sustain an infection. In addition, any reactions to the spike protein would be transient and the GMO would be rapidly cleared by the immune system. The minimal exposure and transient nature of infection would be expected to result in very mild, or negligible symptoms and would also minimise the potential for an adverse immune response to the GMO. Therefore, exposure to the GMO is not expected to result in an infection and would not result in an increased disease burden in humans or animals.

135. As mentioned in Chapter 1, Section 4.1, the SARS-CoV-2 virus enters a host's cells via the ACE2 receptor, which is involved in the renin-angiotensin-aldosterone system. When exposed to the GMO, there is a potential that the spike proteins produced will bind to ACE2, which can prevent the conversion of angiotensin II into angiotensin. This could result in more angiotensin II binding to the ATI1 receptor, which can lead to detrimental effects such as vasoconstriction and enhanced inflammation and/or increased angiotensin II expression in the lungs. However, there has not been any reported cases of such effects. Further, it is very unlikely that the amount of spike protein present in the replicative defective viral vectored vaccine can have a sustained effect on people. To date, vaccines that have used the spike proteins from SARS-CoV-2 have shown a good clinical safety profile (Folegatti et al., 2020; Logunov et al., 2020; Ramasamy et al., 2020; Sadoff et al., 2020b; Voysey et al.; Zhu et al., 2020).

136. Vaccines against SARS-CoV-2 using the full length spike protein in replicative defective viral vectors including HAdV based vaccine have shown the ability to generate neutralising antibodies against SARS-CoV-2 (Folegatti et al., 2020; Logunov et al., 2020; Ramasamy et al., 2020; Sadoff et al., 2020b; Voysey et al.; Zhu et al., 2020). There is potential for these vaccines to cause antibody-dependant enhancement[1]-mediated viral entry or immunopathology via the generation of sub- or

[1] Antibody-dependant enhancement (ADE) can occur when pre-existing sub- or non-neutralising antibodies towards a virus can enhance the viral entry into host's cells during secondary viral infections. This antibody-

non-neutralising antibodies towards the spike protein (Arvin et al., 2020; Su et al., 2020). However, there has not been any reports of ADE associated with these COVID-19 vaccine candidates to date. The administration of convalescent plasma from patients who had recovered from SARS-CoV-2 infection into 20,000 patients who had a high risk of severe COVID-19 disease showed low incidence of serious adverse events (Joyner et al., 2020). A recent study using this GM vaccine in hamsters did not show any evidence of ADE (van der Lubbe et al., 2021). Phase I/IIa results using the GM vaccine has also favours the induction of a Th1 type immune response, whereas the theoretical risk of ADE is associated with a Th2 type response (Sadoff et al., 2020b; Sadoff et al., 2021b). Further, no ADE was observed with inactivated-whole SARS-CoV-1 (Luo et al., 2018) and DNA vaccine expressing SARS-CoV-2 S protein (Arvin et al., 2020). To date, there is no conclusive evidence demonstrating a risk of ADE in humans in relation to SARS-CoV-2 infection.

Conclusion

137. The potential for an unintentional exposure of people and animals to the GMO resulting in increased disease burden in humans and animals is not identified as a risk that could be greater than negligible. Therefore, it does not warrant further detailed assessment.

dependant enhancement mediated viral entry has been mostly documented in flaviviruses (e.g. dengue virus) but also observed in various viral infections such as HIV, Ebola and coronaviruses (e.g. MERS and SARS-CoV-1).

2.4.2 Risk Scenario 2

Risk source	GMO
Causal pathway	Exposure of other people and animals to the GMO as mentioned in Risk Scenario 1 ⬇ Transduction of cells by GMO ⬇ Transduced cells co-infected with AdV ↙ ↘ Complementation of E1 and E3 by AdV ⬇ Production of more replication incompetent GMOs with immune-evasion properties Homologous recombination with AdV in E1, E3 or other regions of high homology ⬇ (i) Formation of replication defective AdV expressing spike protein (E1) **AND** Replication competent GMO without spike protein (E1) **OR** (ii) Replication competent AdV with defective immune evasion properties (E3) **AND** Replication incompetent GMO with immune evasion properties (E3) **OR** (iii) Replication competent AdV or replication incompetent GMO with altered tropism
Potential harm	Adverse immune reactions (e.g., cytokine storm) and/or disease in people or animals

Risk source

138. The source of potential harm for this postulated risk scenario is the GMO.

Causal Pathway

139. The transmission of GMO can occur by the pathways mentioned in Risk Scenario 1 which could potentially result in transduction of host cells. If the person or animal exposed to the GMO has an existing infection of AdVs at the same time of exposure or acquired an AdV infection while the GMO is present, this co-infection could potentially result in complementation and recombination of the GMO with wild-type AdVs and cause an adverse immune reactions.

Complementation of E1 and E3 by AdV

140. HAdV infects over 80% of the human population and the genome of HAdV-D (the largest species of HAdVs) are highly conserved (>90%)(Ismail et al., 2018). Therefore, it is plausible that the E1 and E3 genes could be provided in *trans* from a pre-existing or acquired HAdV infection in persons accidentally exposed to the GMO if a co-infection in the same cell occurs. This could result in complementation by the HAdV leading to replication of the GMOs with immune evasion properties in

the host. However, the seroprevalance of HAdV-D26, appears to be higher in Africa and Asia compared to North America and Europe (Mennechet et al., 2019); and in Australia, the reported prevalence of HAdV infection is very low (Spencer, 2002). Therefore, the probability of the GMO and the wild-type HAdV infecting the same cells at the same time in humans or animals is unlikely. Furthermore, HAdV infections are also self-limiting, decreasing the probability of continuous complementation of GMO by HAdV (Knight et al., 1962; Lichtenstein and Wold, 2004b). Thus, the likelihood that a person with HAdV-D infection that could continuously complement the missing E1 and E3 genes in the GMO is very low.

141. As mentioned in Chapter 1, Section 3.5.1, HAdVs are unable to replicate in animal models (Ismail et al., 2019) and no natural infections of non-human hosts have currently been described. Therefore, the likelihood of that the GMO could replicate in animals as a result of complementation is very low.

Homologous recombination with AdV

142. Recombination is common among circulating wild-type adenoviruses in nature. It is seen as a key driver for adenoviral evolution and viruses in general. Similar to complementation, homologous recombination also requires the person or animals exposed to the GMO to be infected with a wild-type AdV at the same time. Adv are prevalent in respiratory, gastrointestinal or ocular tissue and are unlikely to be commonly present in subcutaneous/skin cells in the case of a needle stick injury during administration. Exposure to the GMO by people or animals via inhalation or contact with mucus tissue is plausible but unlikely as detailed in risk scenario 1. Therefore the likelihood of the GMO to be present simultaneously with a resident Adv in the same cell is highly unlikely.

143. AdV infections are common in humans and are present in other species. Therefore, there is a potential that a person or animal exposed to the GMO is co-infected with AdV. As mentioned in Chapter 1, Section 3.4, homologous recombination is restricted to members of the same species however homologous recombination with closely related adenoviruses species has been observed where high sequence homology occurs (Hoppe et al., 2015; Dehghan et al., 2019). The DNA homology between HAdV species is less than 20% (Ghebremedhin, 2014) and is approximately 94% in HAdV-D species (Robinson et al., 2011a). Therefore, there is a potential of homologous recombination between the GMO and HAdV-D as they belong to the same species. If it was to occur, co-infection and recombination processes could potentially result in the generation of different GM recombinants. These GM recombinants are described in Table 2.

Table 2 Plausible theoretical recombinants of GMO and wild-type Adenoviruses

Recombinant region	Resultant recombinant	Outcome	Likelihood
E1 between • GMO • WT AdV	• Replication competent GMO without E3 gene • Replication incompetent AdV with spike protein	• Replication competent GMO that is still less immune evasive than WT • Replication incompetent AdV expressing spike protein	Unlikely as these regions are not high homology region.

Recombinant region	Resultant recombinant	Outcome	Likelihood
E3 between • GMO • WT AdV	• Replication incompetent GMO with E3 gene • Replication competent AdV without E3	• Replication incompetent GMO with modifed immune-evasive properties • Replication competent AdV without immune-evasive properties (a wild type adenovirus unable to evade the host immune system)	Unlikely
Hypervariable regions (hexon, penton and fiber) between • GMO • WT AdV	• Replication incompetent GMO with different hexon, penton or fiber. • Replication competent AdV without the spike but with different (hexon, penton or fiber)	• Altered tropism and host range of GMO • Altered tropism and host range of AdV	Unlikely

144. The wild-type AdV could receive the spike protein gene from the GMO and gain immuno-stimulatory function. The GMO could regain its E1 gene but lose the gene encoding spike protein and become replication competent. This would result in a replication competent GMO without the spike protein and E3; and a replication incompetent AdV expressing S protein. As discussed in Chapter 1, Section 3.4, the recombination between HAdV-D is suggested to occur only in hypervariable regions of the HAdV-D genome and did not include the E1 region (Robinson et al., 2011a; Robinson et al., 2013). In addition, the method used to insert the transgene into E1 gene of the GMO further decreases the likelihood of recombination with HAdV (Abbink et al., 2007). This further restricts homologous recombination and formation of replication defective HAdV-Ds expressing spike protein or replication competent GMO without spike protein.

145. The GMO could regain its E3 gene and therefore its immune-evasive properties but remain replication incompetent. The resulting GMO would still be cleared by the immune system.

146. Homologous recombination could potentially occur at the hexon, penton and fibre regions of AdV, especially in species D, resulting in the GMO with an altered cell tropism but still remaining replication incompetent.

147. Recombinant replication competent viruses could then be shed from the host and transmitted to other hosts (human or animals) in the environment. These replication competent viruses would not include the S gene and would be similar to a wild type Adenovirus. However, in order for a full reversion into a wild-type virus, multiple recombination events would need to occur and this is highly unlikely.

148. Increased expression of spike protein in the host is highly unlikely to result in the production of novel toxic or allergenic compounds. The genome of the GMO including the introduced genes has been fully sequenced. These proteins are not known to be toxic to humans.

Potential harm

149. If complementation were to occur, the number of replication incompetent GMOs produced in the host cells would increase resulting in increased expression of spike proteins in the host. Similarly, homologous recombination would increase the expression of the introduced genes i.e., spike proteins. The exposed individuals may generate a stronger antibody response for the S glycoprotein of SARS-CoV-2 and also develop T-cell responses. These are not expected to cause harm to affected individuals. If the person exhibits any symptoms of adenoviral infection, effective antiviral treatments can be used to treat the infection.

150. If homologous recombination were to occur it could result in the formation of replication competent HAdV-D26. The person exposed could potentially experience mild respiratory or eye infections depending on the route of exposure as described in Chapter 1, Section 3.1. These infections are self-limiting and rarely need medical intervention. If needed, first line adenoviral antiviral therapies could be used. Theoretically, if homologous recombination in the major capsid proteins (HAdV-D) or other AdV regions with high homology occurs, it could alter the tropism and host range of the virus. However, the risks of potential increased harm are negligible as adenoviruses do not typically cause severe disease and the resultant recombinants will be less pathogenic than the wild-type virus.

Conclusion

151. The exposure of people to a GMO which has acquired the E1 gene, transferred spike proteins to other AdVs or other recombinant viruses resulting in adverse immune response or disease in people or animals is not identified as a risk that could be greater than negligible. Therefore, it does not warrant further assessment.

2.4.3 Risk scenario 3

Risk source	GMO
Causal pathway	Release of GMO into the environment via accidental spill/unused residues (e.g. sewerage, spills) ⬇ Exposure to people or animals ⬇ As per scenario 1-2
Potential harm	Adverse immune reactions (e.g., cytokine storm) and/or disease in people or animals

Risk Source

152. The source of potential harm for this postulated risk scenario is the GMO.

Causal Pathway

153. The GMO could be released in the environment through a spill during transport, storage or disposal where people or animals, including marine or aquatic animals could be exposed to the GMO. This could result in exposure of people and animals to the GMO and could potentially result in adverse immune reactions and/or disease in people and animals.

154. As discussed in Risk Scenario 1, the accidental spills associated with import, transport, storage and disposal have been considered, including the range of measures that are in place that would reduce the chances of GMO being released into the environment.

155. In the event of a spill without correct decontamination with suitable disinfectants, the GMO could potentially persist/survive on surfaces for more than 12 weeks at low humidity (see Chapter 1, Section 3.5.4). In cold water or dark sediments, survival could be up to a few months (see Chapter 1,

Section 3.5.4 and Section 4.3.3). Accidental spillage that is not decontaminated could result in the release of the GMO and/or recombinant viruses into the environment. As AdVs are resistant to UV treatment in wastewater and can survive for a long time, this could lead to the persistence of the GMO and/or recombinant adenoviruses in the environment.

156. As mentioned in Chapter 1, Section 3 and 5.2, HAdV-D26 is a member of the genus *Mastadenovirus* which infects a wide range of mammals including non-human primates, bats, felines, swine, canine, ovine and caprine (Roy et al., 2004; Borkenhagen et al., 2019). Therefore, it is plausible that the GMO could infect other mammals including non-human primates. However, given that the GMO is replication incompetent, exposure to the GMO to other mammals could result in infection but not the replication and multiplication of the GMO.

157. As mentioned above, HAdV infection is limited to mammals only and is not known to infect insects, birds and non-mammalian aquatic organisms. Therefore, the likelihood of HAdVs infecting other species in the Australian environment in highly unlikely.

158. Similar to the parent organism, the GMO could persist in the environment. However, due to its non-replicating nature, the GMO would be unable to maintain a stable presence in the environment for long periods. Further, accidental spill/unused vials if not decontaminated appropriately could result in the survival of the GMO and their presence in the sewerage and subsequently GMO dispersal in the aquatic environment. The impact of survival of the GMO in an aquatic environment is likely to be very low as the GMO is replication incompetent and would eventually degrade.

159. In the unlikely event that GMO is released into sewage water, it will be markedly diluted due to the small quantity of GMO present in a large volume of liquid waste or water. Therefore it is highly unlikely that infection of humans or animals could occur following exposure to an environmental source is.

160. Complementation and recombination could occur in the cells of co-infected animals in a similar way to the host as discussed in Risk Scenario 2.

Potential harm

161. Potential harms in this risk scenario would be the same as considered in the risk scenario 1 and 2 presented above.

Conclusion

162. The potential of GMO to be released into the environment and result in adverse immune reactions or disease in people or other animals is not identified as a risk that could be greater than negligible. Therefore, it does not warrant further assessment.

Section 3 Uncertainty

163. Uncertainty is an intrinsic part of risk analysis[2]. There can be uncertainty in identifying the risk source, the causal linkage to harm, the type and degree of harm, the likelihood of harm or the level of risk. In relation to risk management, there can be uncertainty about the effectiveness, efficiency and practicality of controls.

164. There are several types of uncertainty in risk analysis (Clark and Brinkley, 2001; Hayes, 2004; Bammer and Smithson, 2008). These include:

[2] A more detailed discussion is contained in the Regulator's *Risk Analysis Framework* available from the OGTR website or via Free call 1800 181 030.

- uncertainty about facts:
  - knowledge – data gaps, errors, small sample size, use of surrogate data
  - variability – inherent fluctuations or differences over time, space or group, associated with diversity and heterogeneity
- uncertainty about ideas:
  - description – expression of ideas with symbols, language or models can be subject to vagueness, ambiguity, context dependence, indeterminacy or under-specificity
  - perception – processing and interpreting risk is shaped by our mental processes and social/cultural circumstances, which vary between individuals and over time.

165. Uncertainty is addressed by approaches such as balance of evidence, conservative assumptions, and applying risk management measures that reduce the potential for risk scenarios involving uncertainty to lead to harm. If there is residual uncertainty that is important to estimating the level of risk, the Regulator will take this uncertainty into account in making decisions.

166. Overall, the level of uncertainty in this risk assessment is considered low and does not impact on the overall estimate of risk.

167. Post release review (Chapter 3, Section 4) will be used to address uncertainty regarding future changes to knowledge about the GMO. This is typically used for commercial releases of GMOs, which generally do not have fixed duration.

Section 4 Risk evaluation

168. Risk is evaluated against the objective of protecting the health and safety of people and the environment to determine the level of concern and, subsequently, the need for controls to mitigate or reduce risk. Risk evaluation may also aid consideration of whether the proposed dealings should be authorised, need further assessment, or require collection of additional information.

169. Factors used to determine which risks need treatment may include:

- risk criteria,
- level of risk,
- uncertainty associated with risk characterisation, and
- interactions between substantive risks.

170. Three risk scenarios were identified whereby the proposed dealings might give rise to harm to people or the environment. This included consideration of whether people and animals can be exposed to the GMO while conducting the dealings and whether there is a potential for complementation and recombination of the GMO with other adenoviruses. The potential for GMO to be released into the environment and its effects was also considered.

171. A risk is substantive only when the risk scenario may, because of gene technology, have some chance of causing harm. Risk scenarios that do not lead to harm, or could not reasonably occur, do not represent an identified risk and do not advance in the risk assessment process.

172. In the context of the range of measures already in place, including the operating guidelines and requirements of the other regulatory agencies, and considering both the short and long term, none of these scenarios was identified as representing a substantive risk requiring further assessment. The principal reasons for this include:

- The GMO is replication incompetent which will prevent it from multiplying in other cells;
- The GMO would be restricted to the site of injection and/or draining lymph nodes and would not be shed from the vaccine recipients;

- The likelihood of accidental exposure to the GMO in people not being vaccinated (non-vaccines) would be minimised due to well-established import, transport, storage and disposal procedures; and
- The likelihood of severe disease as a result of complementation and recombination of GMO with other adenoviruses is highly unlikely and the impact of persistence of the small numbers of GMO in the Australian aquatic and terrestrial environment is negligible.

Therefore, any risks to the health and safety of people, or the environment, from the proposed commercial supply of the GM vaccine are considered to be negligible. The *Risk Analysis Framework* (OGTR 2013), which guides the risk assessment and risk management process, defines negligible risks as insubstantial with no present need to invoke actions for their mitigation. No controls are required to treat these negligible risks. Hence, the Regulator considers that the dealings involved in this proposed release do not pose a significant risk to either people or the environment[3]

[3] As none of the proposed dealings are considered to pose a significant risk to people or the environment, Section 52(2)(d)(ii) of the Act mandates a minimum period of 30 days for consultation on the RARMP.

Chapter 3 Risk management plan

Section 1 Background

173. Risk management is used to protect the health and safety of people and to protect the environment by controlling or mitigating risk. The risk management plan addresses risks evaluated as requiring treatment and considers limits and controls proposed by the applicant, as well as general risk management measures. The risk management plan informs the Regulator's decision-making process and is given effect through proposed licence conditions.

174. Under section 56 of the Act, the Regulator must not issue a licence unless satisfied that any risks posed by the dealings proposed to be authorised by the licence are able to be managed in a way that protects the health and safety of people and the environment.

175. All licences are subject to three conditions prescribed in the Act. Section 63 of the Act requires that each licence holder inform relevant people of their obligations under the licence. The other statutory conditions allow the Regulator to maintain oversight of licensed dealings: Section 64 requires the licence holder to provide access to premises to OGTR inspectors and Section 65 requires the licence holder to report any information about risks or unintended effects of the dealing to the Regulator on becoming aware of them. Matters related to the ongoing suitability of the licence holder are also required to be reported to the Regulator.

176. The licence is also subject to any conditions imposed by the Regulator. Examples of the matters to which conditions may relate are listed in Section 62 of the Act. Licence conditions can be imposed to limit and control the scope of the dealings. In addition, the Regulator has extensive powers to monitor compliance with licence conditions under Section 152 of the Act.

Section 2 Risk treatment measures for substantive risks

177. The risk assessment of risk scenarios listed in Chapter 2 concluded that there are negligible risks to people and the environment from the proposed supply of the GMO. These risk scenarios were considered in the context of the proposed receiving environment and the Australia-wide release. The risk evaluation concluded that no containment measures are required to treat these negligible risks.

Section 3 General risk management

178. All DIR licences issued by the Regulator contain a number of conditions that relate to general risk management. These include conditions relating to:

- applicant suitability
- testing methodology
- identification of the persons or classes of persons covered by the licence
- reporting structures; and
- access for the purpose of monitoring for compliance.

3.1 Applicant suitability

179. In making a decision whether or not to issue a licence, the Regulator must have regard to the suitability of the applicant to hold a licence. Under Section 58 of the Act, matters that the Regulator must take into account include:

- any relevant convictions of the applicant
- any revocation or suspension of a relevant licence or permit held by the applicant under a law of the Commonwealth, a State or a foreign country

- the capacity of the applicant to meet the conditions of the licence.

180. If a licence were issued, the conditions would include a requirement for the licence holder to inform the Regulator of any circumstances that would affect their suitability.

181. In addition, any applicant organisation must have access to a properly constituted Institutional Biosafety Committee and be an accredited organisation under the Act.

3.2 Testing methodology

182. If a licence were issued, Janssen-Cilag would be required to provide a method to the Regulator for the reliable detection of the GMO, and the presence of the introduced genetic materials in a recipient organism. This methodology would be required prior to conducting any dealings with the GMO.

3.3 Identification of the persons or classes of persons covered by the licence

183. If a licence were issued, any person, including the licence holder, could conduct any permitted dealing with the GMO.

3.4 Reporting requirements

184. If issued, the licence would oblige the licence holder to immediately report any of the following to the Regulator:

- any additional information regarding risks to the health and safety of people or the environment associated with the dealings
- any contraventions of the licence by persons covered by the licence
- any unintended effects of the release.

185. The licence holder is also obliged to submit an Annual Report containing any information required by the licence.

186. There are also provisions that enable the Regulator to obtain information from the licence holder relating to the progress of the commercial release (see Section 4, below).

3.5 Monitoring for compliance

187. The Act stipulates, as a condition of every licence, that a person who is authorised by the licence to deal with a GMO, and who is required to comply with a condition of the licence, must allow the Regulator, inspectors or other person authorised by the Regulator, to enter premises where a dealing is being undertaken for the purpose of monitoring or auditing the dealing.

188. In cases of non-compliance with licence conditions, the Regulator may instigate an investigation to determine the nature and extent of non-compliance. The Act provides for criminal sanctions of large fines and/or imprisonment for failing to abide by the legislation, conditions of the licence or directions from the Regulator, especially where significant damage to the health and safety of people or the environment could result.

Section 4 Post release review

189. Regulation 10 requires the Regulator to consider the short and the long term when assessing risks. The Regulator takes account of the likelihood and impact of an adverse outcome over the foreseeable future, and does not disregard a risk on the basis that an adverse outcome might only occur in the longer term. However, as with any predictive process, accuracy is often greater in the shorter rather than longer term.

190. For the current application for a DIR licence, the Regulator is including conditions that require ongoing oversight in order to provide feedback on the findings of the RARMP and ensure the

outcomes remain valid for future findings or changes in circumstances. If a licence was issued, this ongoing oversight would be achieved through PRR activities. The three components of PRR are:

- adverse effects reporting system (Section 4.1)
- requirement to monitor specific indicators of harm (Section 4.2)
- review of the RARMP (Section 4.3).

The outcomes of these PRR activities may result in no change to the licence or could result in the variation, cancellation or suspension of the licence.

4.1 Adverse effects reporting system

191. Any member of the public can report adverse experiences/effects resulting from a GMO to the OGTR through the Free-call number (1800 181 030), mail (MDP 54 – GPO Box 9848, Canberra ACT 2601) or via email to the OGTR inbox (ogtr@health.gov.au). Reports can be made at any time on any DIR licence. Credible information would form the basis of further investigation and may be used to inform a review of a RARMP (see Section 4.3 below) as well as the risk assessment of future applications involving similar GMOs.

4.2 Requirement to monitor specific indicators of harm

192. Collection of additional specific information on an intentional release provides a mechanism for 'closing the loop' in the risk analysis process and for verifying findings of the RARMP, by monitoring the specific indicators of harm that have been identified in the risk assessment.

193. The term 'specific indicators of harm' does not mean that it is expected that harm would necessarily occur if a licence was issued. Instead, it refers to measurement endpoints which are expected to change should the authorised dealings result in harm. Should a licence be issued, the licence holder would be required to monitor these specific indicators of harm as mandated by the licence.

194. The triggers for this component of PRR may include risk estimates greater than negligible or significant uncertainty in the risk assessment.

195. The characterisation of the risk scenarios discussed in Chapter 2 did not identify any risks greater than negligible. Therefore, they were not considered substantive risks that warranted further detailed assessment. Uncertainty is considered to be low. No specific indicators of harm have been identified in this RARMP for application DIR 182. However, specific indicators of harm may also be identified during later stages, e.g. following the consideration of comments received on the consultation version of the RARMP, or if a licence were issued, through either of the other components of PRR.

196. Conditions have been included in the licence to allow the Regulator to request further information from the licence holder about any matter to do with the progress of the release, including research to verify predictions of the risk assessment.

4.3 Review of the RARMP

197. The third component of PRR is the review of RARMPs after a commercial/general release licence is issued. Such a review would take into account any relevant new information, including any changes in the context of the release, to determine if the findings of the RARMP remained current. The timing of the review would be determined on a case-by-case basis and may be triggered by findings from either of the other components of PRR or be undertaken after the authorised dealings have been conducted for some time. If the review findings justified either an increase or decrease in the initial risk estimate(s), or identified new risks to people or to the environment that require management, this could lead to changes to the risk management plan and licence conditions.

Section 5 Conclusions of the consultation RARMP

198. The risk assessment concludes that the proposed commercial release of this GM COVID-19 vaccine poses negligible risks to the health and safety of people or the environment as a result of gene technology.

199. The risk management plan concludes that these negligible risks do not require specific risk treatment measures. However, if a licence were to be issued, general conditions are proposed to ensure that there is ongoing oversight of the release.

Chapter 4 Draft licence conditions

Section 1 Interpretations and Definitions

1. In this licence:

   (a) unless defined otherwise, words and phrases used have the same meaning as they do in the Act and the Gene Technology Regulations 2001 (the Regulations);

   (b) words denoting a gender include any other gender;

   (c) words in the singular include the plural and words in the plural include the singular;

   (d) words denoting persons include a partnership and a body whether corporate or otherwise;

   (e) references to any statute or other legislation (whether primary or subordinate) are a reference to a statute or other legislation of the Commonwealth of Australia as amended or replaced from time to time and equivalent provisions, if any, in corresponding State law, unless the contrary intention appears;

   (f) where any word or phrase is given a defined meaning, any other part of speech or other grammatical form in respect of that word has a corresponding meaning;

   (g) specific conditions prevail over standard conditions to the extent of any inconsistency.

2. In this licence:

'**Act**' means the *Gene Technology Act 2000* (Cth) or the corresponding State legislation under which this licence is issued.

'**Annual Report**' means a written report provided to the Regulator by the end of September each year containing all the information required by this licence to be provided in the Annual Report.

'ARTG' means the Australian Register of Therapeutic Goods maintained in accordance with the *Therapeutic Goods Act 1989*.

'**GM**' means genetically modified.

'**GMO**' means the genetically modified organism that is the subject of the dealings authorised by this licence.

'NLRD' is a Notifiable low risk dealing. Dealings conducted as an NLRD must be assessed by an institutional biosafety committee (IBC) before commencement and must comply with the requirements of the Gene Technology Regulations 2001.

'**OGTR**' means the Office of the Gene Technology Regulator.

'**Regulator**' means the Gene Technology Regulator.

Section 2 Licence conditions and obligations

3. This licence remains in force until it is suspended, cancelled or surrendered. No dealings with the GMO are authorised during any period of suspension.

4. The licence holder is Janssen-Cilag Pty Ltd.

5. Any person, including the licence holder, may conduct any authorised dealing(s) with the GMO.

6. The dealings authorised by this licence are:

   a) import of the GMOs;

   b) transport of the GMOs;

   c) disposal of the GMOs;

and the possession (including storage) and supply of the GMOs for the purposes of, or in the course, of any of these dealings.

Note: Use of the GMO for therapeutic purposes is not covered by the Gene Technology Act 2000 and therefore this licence is not required to authorise such use. The GMOs are also subject to regulation by other federal and state departments and agencies, including the Therapeutic Goods Administration and the Department of Agriculture, Water and the Environment. These other departments and agencies may impose further requirements for, or limitations on, the use of the GMO or these dealings.

7. This licence does not apply to dealings with the GMOs conducted as a Notifiable Low Risk Dealing (NLRD) or pursuant to another authorisation under the Act.

Note: Dealings conducted as an NLRD must be assessed by an Institutional Biosafety Committee (IBC) before commencement and must comply with the requirements of the Regulations

8. Dealings with the GMO may be conducted in all areas of Australia.

9. The licence authorises dealings with the GMO described in **Attachment A**.

Note: Attachment A is not included in the draft licence.

2.1 Obligations of the Licence Holder

10. The licence holder must immediately notify the Regulator if any of its contact details change.

Note: Please address correspondence to OGTR.M&C@health.gov.au

Prior to issuing a licence, the Regulator considers suitability of the applicant to hold a licence. The following conditions address ongoing suitability of the licence holder.

11. The licence holder must, at all times, remain an accredited organisation in accordance with the Act and must comply with its instrument of accreditation.

12. The licence holder must:

(a) inform the Regulator immediately in writing, of:

i. any relevant conviction of the licence holder; and

ii. any revocation or suspension of a licence or permit held by the licence holder under a law of the Australian Government, a State or a foreign country, being a law relating to the health and safety of people or the environment; and

iii. any event or circumstances that would affect the capacity of the holder of this licence to meet the conditions in it; and

(b) provide any information related to the licence holder's ongoing suitability to hold a licence, if requested, within the stipulated timeframe.

13. The licence holder must inform any person covered by this licence, to whom a particular condition of the licence applies, of the following:

(a) the particular condition (including any variations of it); and

(b) the cancellation or suspension of the licence; and

(c) the surrender of the licence.

2.2 Provision of new information to the Regulator

Licence conditions are based on the risk assessment and risk management plan developed in relation to the application using information available at the time of assessment. The following condition

requires that any new information that may affect the risk assessment is communicated to the Regulator.

14. The licence holder must inform the Regulator if the licence holder becomes aware of:

(a) additional information as to any risks to the health and safety of people, or to the environment, associated with the dealings authorised by the licence; or

(b) any contraventions of the licence by a person covered by the licence; or

(c) any unintended effects of the dealings authorised by the licence.

Note: The Act requires, for the purposes of the above condition, that:

(a) the licence holder will be taken to have become aware of additional information of a kind mentioned in paragraph 14 if he or she was reckless as to whether such information existed; and

(b) the licence holder will be taken to have become aware of contraventions, or unintended effects, of a kind mentioned in paragraph 14, if he or she was reckless as to whether such contraventions had occurred, or such unintended effects existed.

Note: Contraventions of the licence may occur through the action or inaction of a person.

15. If the licence holder is required to inform the Regulator under condition 14, the Regulator must be informed without delay.

Note: An example of informing without delay is contact made at the time of the incident via the OGTR free call phone number 1800 181 030, which provides emergency numbers for incidents that occur out of business hours.

16. If at any time the Regulator requests the licence holder to collect and provide information about any matter to do with the progress of the dealings authorised by this licence, including but not confined to:

(a) additional information as to any risks to the health and safety of people, or to the environment, associated with the dealings authorised by the licence, whether or not the licence holder has provided information to the Regulator under condition 14(a);

(b) any contraventions of the licence by a person covered by the licence, whether or not the licence holder has provided information to the Regulator under condition 14(b);

(c) any unintended effects of the dealings authorised by the licence, whether or not the licence holder has provided information to the Regulator under condition 14(c);

(d) research, including by way of survey, to verify predictions of the risk assessment, or for any purpose related to risks to the health and safety of people, or to the environment;

(e) scientific literature and reports in respect of the GMO authorised by this licence, for a nominated period;

(f) details of any refusals of applications for licences or permits (however described) to deal with the GMO made pursuant to the regulatory laws of a foreign country;

and the request is reasonable, having regard to consistency with the Act and relevance to its purpose, then the licence holder must collect the information and provide it to the Regulator at a time and in the manner requested by the Regulator.

Note: The Regulator may invite the licence holder to make a submission on the reasonability of a request by the Regulator to collect and provide information relevant to the progress of the dealings with the GMO.

2.3 Obligations of persons covered by the licence

17. If a person is authorised by this licence to deal with the GMOs and a particular condition of this licence applies to the dealing by that person, the person must allow the Regulator, or a person authorised by the Regulator, to enter premises where the dealing is being undertaken, for the purposes of auditing or monitoring the dealing.

Section 3 Reporting and Documentation Requirements

3.1 Notification of Authorisation by the Therapeutic Goods Administration

18. If the GMOs are included on the ARTG, the licence holder must notify the Regulator in writing within 14 days of registration.

19. The licence holder must notify the Regulator in writing of any subsequent amendments to the conditions of the ARTG registration involving the pattern of usage, handling, storage, transport or disposal of the GMOs, within 14 days of the change occurring.

3.2 Annual Report

20. The licence holder must provide an Annual Report to the Regulator by the end of September each year covering the previous financial year. An Annual Report must include:

(a) information about any adverse impacts, unintended effects, or new information relating to risks, to human health and safety or the environment caused by the GMOs or material from the GMOs;
(b) information about the numbers of GM vaccine doses imported and distributed to each State and Territory.

3.3 Testing methodology

21. At least 14 days prior to conducting any dealings with the GMO, the licence holder must provide to the Regulator a written methodology to reliably detect the GMO, or the presence of the genetic modifications described in **Attachment A** in a recipient organism or environmental sample. The detection method(s) must be capable of identifying, to the satisfaction of the Regulator, each genetic modification event described in **Attachment A**.

Note: Please address correspondence to OGTR.M&C@health.gov.au

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Appendix A: Summary of submissions

The Regulator received several submissions from prescribed experts, agencies and authorities[4] on matters relevant to preparation of the RARMP. All issues raised in submissions relating to risks to the health and safety of people and the environment were considered. These issues, and where they are addressed in the consultation RARMP, are summarised below.

Submission	Summary of issues raised	Comment
1	Direct environmental risks from the proposed release of the GM virus are expected to be negligible. However, due to the potential significant scale of use of COVID-19 adenoviral vaccines in the coming years, it is recommended that the following factors be considered in the RARMP: • Shedding duration; • Persistence in the environment; • Exposure of organisms; • Host range of the GM virus; and Potential recombination with non-GM wild type viruses	The potential for viral replication shedding, persistence, host range and recombination have been discussed throughout Chapter 1 (Section 3.4, 3.5.1, 3.5.2, 3.5.4, 4.3.2 and 4.3.3) and Chapter 2 (Risk scenario 2 and 3).
2	At this stage, the department does not have specific advice on risks to health and safety of people and the environment to be considered in the development of the RARMP.	Noted.
3	Members noted, that although the parent organism is a human pathogen, the AdVac® technology was previously used for vaccine development for other diseases. They support the licence application and look forward to release of the RARMP.	Noted.
4	Recommends that the OGTR considers the potential shedding of viable adenovirus vaccine vector from immunised humans into the sewerage system; the potential risk of recombination between the vaccine vector and human adenovirus; and associated risks of harm to human health once in the receiving environment. This could potentially be addressed by requiring Janssen-Cilag to provide analytical data from stool samples obtained from vaccine recipients during the clinical trials, to detect the presence/absence of viable virus that could be shed to sewer.	Noted.
5	**Draft recommendations** The committee agrees that the following should be included in the RARMP: potential accidental exposure of humans and other organism to the GMO resulting in harm, potential for complementation and recombination of the GMO and other	Noted.

[4] Prescribed expects, agencies and authorities include GTTAC, State and Territory Governments, Australian government agencies and the Minister for the Environment.

Submission	Summary of issues raised	Comment
	adenoviruses and potential for GMO to be harmful to the environment.	
	The committee also suggested to consider risks associated with: • possible integration of the adenoviral DNA into human genomes; and • appropriate methods for decontaminating any spills.	The potential for random integration of vector DNA is discussed in Chapter 1 (Section 3.4 and 4.3.1) and Chapter 2 (Section 2.2). Appropriate decontamination methods are discussed in Chapter 1, Section 3.5.4.